DERIVATIVES OF PIPERAZINE IX
SYNTHESES WITH ALKENE OXIDES

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PREFACE

The material contained in this dissertation is presented in a format similar to that used for the articles in "Chemical Reviews"; this was found to be most satisfactory for proper interrelation of the several parts of the investigation. The manner of listing references is the customary one for technical works in organic chemistry of comparable length and scope. Journal abbreviations are the official ones of "Chemical Abstracts".

In conformity with present usage in research communications, all temperatures are of the centigrade scale; and the centigrade symbol is omitted.

The melting points are capillary melting points. The symbol "(corr.)" is used after every corrected melting point. The thermometers used for obtaining the melting points were calibrated against a set of thermometers standardized by the Bureau of Standards.

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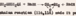
I. INTRODUCTION

The alkene oxides are highly reactive compounds which find extensive use in organic syntheses. The classical method for the preparation of alkene oxides has been the removal of hydrogen and halogen from 1,2-halohydrins by the use of strong base. For example, ethene chlorohydrin has been prepared by bubbling ethene through chlorine water:

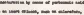
$$CH_2=CH_2 + HOCl \rightarrow CH_2OHCH_2Cl$$

Subsequent treatment with strong sodium hydroxide solution yields ethene oxide:



$$CH_2OHCH_2Cl + NaOH \rightarrow \underset{O}{CH_2-CH_2} + NaCl$$

The Prileschajew reaction (114,115) made it possible to prepare many alkene oxides which could not be synthesized by the older method. High yields are obtained by this reaction, which involves direct introduction of an oxygen atom into the ethene group of a molecule containing this type of unsaturation by means of perbenzoic acid. The reaction is carried out in an inert diluent, such as chloroform, suitably at 0°:

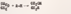


$$RCH=CHR + \phi\underset{o}{COOH} \rightarrow \underset{O}{RCH-CHR} + \phi COOH$$

Thus, by this method the oxides of highly reactive molecules such as isoprene may be prepared. This method will become of increasing economic importance as perbenzoic becomes more available on the market. It is anticipated that electrolytic oxidation methods will provide access to an abundance of perbenzoic acid.

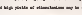
In recent years the lower alkene oxides, particularly the oxides of ethene and propene, have been made available in almost unlimited amounts by the direct catalytic air oxidation[1] of the corresponding olefin hydrocarbons. The preferred catalyst is metallic silver, and the reaction suitably is carried out at a temperature ranging from 200° to 400° C.

Ethene oxide and substituted ethene oxides react readily with compounds containing certain types of reactive hydrogen, yielding hydroxyethyl- and substituted hydroxyethyl- derivatives:



$$\begin{matrix} CH_2 \\ CH_2 \end{matrix}\!\!>O + R\text{-}H \longrightarrow \begin{matrix} CH_2OH \\ CH_2R \end{matrix}$$

The class of compounds R-H includes acids, alcohols, water, ammonia and amides. Reaction with hydroxyl hydrogen is effectively inhibited by a basic medium, and high yields of ethanolamines may be obtained:



$$>N\text{-}H + \begin{matrix} CH_2 \\ CH_2 \end{matrix}\!\!>O \longrightarrow \;>NCH_2CH_2OH$$

Indeed, due to the preferential reaction with amine hydrogen, water or alcohol may be used as reaction medium.

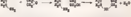
It becomes apparent that the ethene oxides should prove to be seeable starting materials for syntheses in the field of piperazines. Bain and Pollard (9, 10, 11) have synthesized certain substituted piperazines from amino-alcohols derived from ethene oxide. Various investigations have been made on the reactions of piperazine with certain ethene oxides; these will be reviewed later.

---

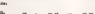
[1] Research on the synthesis of ethene oxide by the catalytic oxidation of ethene is contained mainly in the patent literature (24, 46, 48, 58, 34, 35, 36, 37, 63, 96, 97, 104, 131).

It is the purpose of the present investigation to provide economic syntheses of piperazine and substituted piperazines by the use of ethene oxide and substituted ethene oxides as intermediates, and to further utilize ethene oxides for the economic synthesis of useful piperazine derivatives.

Thus, the application of ethene oxides to syntheses in the piperazine series the two phases. One of these is the synthesis of the piperazine ring itself. synthesis by the following route was investigated:



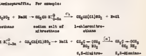
In addition to an ethene oxide, a required starting material is ethene diamine or a substituted ethene diamine, e. g., propene diamine. These are available from such fundamental starting materials as natural gas (propane), air (nitrogen), water (hydrogen) and salt (chlorine and sodium hydroxide), i. e., ethene, chlorine, ammonia and sodium hydroxide:



Interest in the basic reaction of an ethene oxide with a 1,2-diamine is enhanced by the recent availability of nitroparaffins, obtained by vapor phase nitration of paraffin hydrocarbons (Commercial Solvents Corp.). 1,2-diamines are obtainable by the following series of reactions:

Nitroparaffin + chlorine + sodium hydroxide → chloronitroparaffin;

Chloronitroparaffin + nitroparaffin + sodium hydroxide → dinitroparaffin, which on reduction yields the corresponding diaminoparaffin. For example:



$$CH_3CH_2NO_2 + NaOH \rightarrow CH_3CH{=}N\begin{smallmatrix}\nearrow O\\ O{-}Na\end{smallmatrix} \xrightarrow{Cl_2} CH_3CH(Cl)NO_2 + NaCl$$

nitroethane — sodium salt of nitroethane — 1-chloronitroethane

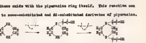
$$CH_3CH{=}N\begin{smallmatrix}\nearrow O\\ O{-}Na\end{smallmatrix} + CH_3CH(Cl)NO_2 \rightarrow NaCl + \underset{NO_2}{CH_3CH}-\underset{NO_2}{CHCH_3} \xrightarrow{[H]} \underset{NH_2}{CH_3CH}-\underset{NH_2}{CHCH_3}$$

2,3-dinitrobutane — 2,3-diaminobutane

Illustrative of the diamines available from the three nitroparaffins (nitroethane, 1-nitropropane, and 2-nitropropane) are the following: 2,3-diaminobutane, 3,4-diaminohexane, 2,3-diamino-2,3-dimethylbutane, 2,3-diaminopentane, etc.

Thus, it may be seen that the above general method for the synthesis of the piperazine ring opens a route to an almost unlimited number of C-substituted piperazines.

The second phase of the present investigation is the reaction of an ethane oxide with the piperazine ring itself. This reaction can lead to mono-substituted and di-substituted derivates of piperazine.



These aminoalcohols are starting materials for many new and useful compounds.

II. DISCUSSION AND EXPERIMENTAL

A. The Synthesis of Piperazine

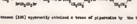
1. Review of the Literature

Piperazine, first prepared in 1853 (41), has been the subject of a large volume of research in the eighty-nine years it has been known. Numerous uses have been developed for piperazine and piperazine derivatives. Use is made of piperazine as a reagent for preparing solid derivatives of fatty acids for identification purposes (108); the piperazine salts of the fatty acids have sharp melting points which are characteristic. Of the nine patents relating to products derived from piperazine which have been granted within the past fifteen years, six (40, 51, 70, 106, 118, 153) relate to medicinals; one (130) to a series of local anesthetics; one (17) to the use of piperazine as a corrosion inhibitor; and one (18) to a series of emulsifying and wetting agents. Siedebach and Weigand (15) suggest the use of piperazine in emulsions.

A potential use of piperazine which may soon utilize millions of pounds of piperazine per year is as a source of the pyrazine ring for the synthesis of sulfapyrazine. The methods of pyrazine synthesis are unsatisfactory in general, and it may be necessary to resort to catalytic dehydrogenation of piperazines as the source of pyrazines. Sulfapyrazine was synthesized in 1941 by Ellingson (48); the recent preliminary report by Ruegsegger and co-workers (121) upon the pharmacological action of sulfapyrazine indicates that this addition to the family of sulfanilamide drugs will become of wide application in pneumonia therapy.

Since the initial synthesis of piperazine, numerous methods for manufacturing piperazine have been published. Nevertheless, up to the time the present investigation was started, there were no published methods for the synthesis of piperazine which were economically feasible. Consequently piperazine has remained high in price, sometimes not being available on the market. At the present time there is no piperazine on the market. However, to the surprise of the author, within the few years during which this research project has been carried on, there have appeared six patents (21, 22, 63, 81, 140, 141) relating to three different processes for the commercial production of piperazine. In addition a patent application has been filed in the United States Patent Office based upon the process which is described in the pages to follow.

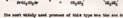
Piperazine was first obtained by Cloëz (41) in investigating the reaction of alcoholic ammonia with ethene chloride and ethene bromide:



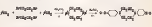
$$NH_3 + \begin{matrix} BrCH_2CH_2Br \\ BrCH_2CH_2Br \end{matrix} + NH_3 \longrightarrow Br.\overset{+}{N}H_2\begin{matrix} CH_2CH_2 \\ CH_2CH_2 \end{matrix}\overset{+}{N}H_2.\overset{-}{Br} \xrightarrow{NaOH} HN\begin{matrix} CH_2CH_2 \\ CH_2CH_2 \end{matrix}NH$$

Natanson (105) apparently obtained a trace of piperazine by the treatment of ethene chloride with alcoholic ammonia. The reaction also was investigated by Hofmann (66). However, this reaction is of little value for the synthesis of piperazine, for piperazine is only a minor product; various ethene polyamines, such as ethene diamine, diethene triamine, and triethene tetramine are formed in the same process (67). A variant of this method was the synthesis of piperazine by Sieber (129), the prepared it by reaction of ethene diamine and ethene bromide. Sanna and Oliverio (122) recently have described an improved process using the ethene bromide-ammonia method, involving the use of very concentrated ammonia.

Processes were developed for the synthesis of piperazine which gave somewhat better yields than the direct alkylation of ammonia. These procedures involved the alkylation of a compound RNH_2 containing a primary amino group by means of ethene dihalide and subsequent removal of the group R by various means.



The most widely used process of this type was the one developed in 1891 by Bischler (14). Bischler applied the known reaction, the alkali hydrolysis of nitroso-substituted arylamines, to the preparation of piperazine by splitting N,N'-bis-(p-nitrosophenyl)-piperazine with alcoholic potassium hydroxide:



The intermediate dinitroso- compound had been prepared previously by Morley (101) through treatment of N,N'-diphenylpiperazine with sodium nitrite and dilute hydrochloric acid. Sodium carbonate was used as a means of removing HBr in the ring closure reaction between aniline and ethene bromide.

Various German patents relating to this process have been issued. One of these (56) utilizes distillation with alcoholic potassium hydroxide or heating with an alkaline earth hydroxide in a closed vessel, and another (57), boiling with dilute alkali as the method of hydrolysis of the dinitroso compound. A third process (58) describes the preparation of piperazine by the gradual introduction of an alkaline solution of sodium nitrite and N,N'-bis-(p-hydroxyphenyl)-piperazine into 10% HCl with cooling, followed by hydrolysis.

Morera (100) describes a procedure for which good results are claimed, using aniline and ethene bromide boiled together for three hours; the base is liberated with soda and extracted with benzene. The extract is distilled to remove benzene, then vacuum distilled; the product is nitrosified with HCl-$NaNO_2$-ice and finally is hydrolyzed with sodium hydroxide solution.

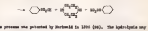
In a recent article Sanna and Oliverio (122) described a shortened process utilizing alkylation of p-nitrosoaniline with ethene bromide. The p-nitrosophenol obtained upon hydrolysis could be reconverted to p-nitrosoaniline.

The hydrolysis of aromatic nitroso derivatives is greatly facilitated by treatment with sodium bisulfite or some other form of sulfur dioxide, according to one patent (27). Sulfamic acid derivatives are formed which readily rearrange with loss of the amino group. A patent issued to Volkmann (12, 130) applied this method to the hydrolysis of N,N'-bis-(p-nitrosophenyl)-piperazine. Pratt and Young gave details of an improved synthesis of piperazine from aniline and ethene bromide, which utilized the sodium bisulfite hydrolysis (112). One process (26) yielded piperazine by treating sulfonic acids of nitrosified diphenyl piperazine with alkali. A patent issued to Majert (93, 94) stated that a sulfonic acid, preferably a polysulfonic acid, of a diaryl piperazine could be hydrolyzed by alkali to yield piperazine. Bucherer (23) reported that a small yield of piperazine was obtained by sulfonation of N,N'-di-α-naphthylpiperazine with sulfuric acid monohydrate and treatment of the sulfonic acid with bisulfite in sodium hydroxide solution in a sealed tube at 145-160°.

Other aryl-substituted piperazines have been hydrolyzed with the formation of piperazine. 1,4-Dibenzylpiperazine, prepared by Gabriel and Stelzner (57) by heating β-bromethyl benzylamine with excess alkali, may be split by means of 10% hydrochloric acid at 100° (56). Majert (93) has prepared piperazine by hydrolysis of various aryl-disubstituted piperazines by means of alkali and steam-distilling the piperazine into an acid. α- or β-dinaphthylpiperazine may be hydrolyzed by heating with acids or with a solution of calcium chloride or zinc chloride at 250° (56).

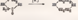
The aryl groups of a diarylpiperazine may be removed by means other than hydrolysis. N,N'-bis-(p-aminophenyl)-piperazine suspended in dilute sulfuric acid yielded piperazine by treatment with sodium dichromate (55); the aminophenyl groups were oxidized.

Another method of piperazine synthesis involves the alkylation of an aryl sulfonamide with ethene dihalide, followed by hydrolysis of the diarylsulfonyl piperazine:

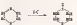


This process was patented by Markwald in 1896 (98). The hydrolysis may be carried out by autoclaving with dilute acid at 200-250° (31); by means of conc. sulfuric acid in an open vessel at 180-200° (31); by the gradual introduction of sodium into a boiling amyl alcohol suspension of the sulfonamide, followed by steam distillation (33); or by heating the dibenzenesulfonylpiperazine with chlorosulfonic acid at about 150° and pouring the melt into water (39). Vinaver (133) gave directions for a process based upon toluene sulfonamide, the intermediate di-p-toluenesulfonyl piperazine having been hydrolyzed with sulfuric acid.

Other six-membered rings containing nitrogen in the 1- and 4-positions may be reduced to piperazine. The reduction of 2,5-diketopiperazine was accomplished by means of zinc dust and aqueous-alcoholic sodium hydroxide and by reduction in anhydrous amyl alcohol solution with sodium (20). Abderhalden and co-workers (1) investigated the reduction of 2,5-diketopiperazine, glycine anhydride, with various agents, including zinc in acetic acid, zinc plus hydrochloric acid, Devarda's alloy plus dilute alkali, sodium and alcohol, and calcium and water in the presence of carbon dioxide. They found electrolytic reduction, using mercury electrodes, to be less satisfactory than the other methods tried. However, Wrede, Brach and Keil (145) report that electrolytic reduction is the best method of reducing the cyclic lactim to piperazine.



A yield of 27% was obtained. Wolff (148) reduced pyrazine, the aromatic piperazine ring, to piperazine by means of sodium and alcohol:

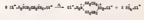


Numerous direct alkylation methods have been attempted which eliminate the necessity of forming an intermediate requiring hydrolysis, as is the case in the preparations which require the formation of a dinitrosodiarylpiperazine or a diarylsulfonylpiperazine. The expense, labor, and low yields attendant with processes in which intermediates are formed are obvious. The hydrolysis which is required in such processes make it necessary to concentrate small amounts of piperazine from large volumes of reaction mixture, usually by steam distillation into an acid and evaporation of the distillate to dryness to recover the piperazine salt. An early patent (80) described the synthesis of piperazine by heating at 250-300° sodium glycollate with an acid derivative of ethylene diamine, suitably N,N'-diacetylethane diamine. The basis of another process (84) was the heating of sodium compounds of diacylethane diamines with anhydrous glycol or ethane bromide at 200°, by refluxing the reactants in xylene solution.

Garelli and Racciu (58) stated that a 90% yield of piperazine may be obtained by dehydrating ethanolamine with an excess of 90% sulfuric acid, heating at 90-140° for a short time. However, Rollins and Calderwood (119) were unable to obtain any piperazine by such a procedure; the only product the latter workers could isolate was β-aminoethanesulfonic acid.

A patent granted recently to Gresberg (68) described the synthesis of piperazine by heating ethene diamine with an ester of the type $ROCH_2CH_2R$, such as ethene glycol monoacetate, by heating in the range 200° to 300°, suitably for twenty-four hours. A condensation catalyst such as zinc chloride could be added.

The reactions which involve the alkylation of an amine with an amine with elimination of ammonia have been applied to the synthesis of piperazine. As long ago as 1888 Ladenburg (88) and Abel (89) prepared piperazine by heating the hydrochloride of ethene diamine:



$$2\ Cl^-.H_3\overset{+}{N}CH_2CH_2\overset{+}{N}H_3.Cl^- \xrightarrow{\Delta} Cl^-.H_2\overset{+}{N}\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}\overset{+}{N}H_2.Cl^- + 2\ \overset{+}{N}H_4.Cl^-$$

Hofmann (68), investigating the reaction further, found that the hydrochloride of piperazine readily is formed by heating the hydrochloride of diethene triamine or of triethene tetramine; the other product was ammonium chloride. Ethene diamine hydrochloride also yielded piperazine, but not with the same ease. Recently Wilson (140, 141) and the Carbide and Carbon Chemicals Corporation (81, 82) have been granted American and foreign patents on this process. Diethene triamine and one of its hydrohalides are heated under pressure to at least 220°, and piperazine was recovered by distillation. Apparently the only novel feature of the Wilson patent was the use of less than the equivalent amount of hydrogen chloride in the reaction mixture of diethene triamine and hydrogen chloride.

The process of Kyrides (81) was the splitting of ammonia from diethene triamine by a catalytic means, with formation of piperazine. The reactant was heated at 200-300° for twenty-four hours in the presence of the catalyst, which could be reduced nickel or platinum, cobalt, copper, etc., in finely divided condition. It was claimed that any other polyethene polyamine or ethene diamine could be used. Yields of 80% were claimed; but it has been found in actual practice that a yield not higher than 50% should be expected.

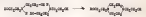
The experimental work in the pages to follow, upon the synthesis of piperazines by catalytic dehydration of hydroxyethyl ethene diamines, is the basis of a patent application (109). These experiments were carried out in liquid phase.

3. The Catalytic Alkylation Method

The vapor-phase catalytic alkylation of aromatic amines with alcohols has been investigated by Mailhe and de Godon (92), by Brown and Reid (18), and by Shuikin and co-workers (129, 130). High yields are obtainable. Effective catalysts are suitably activated oxides of aluminum, titanium, thorium, and iron, and silica gel. Shuikin and co-workers (127) have prepared amines by the simultaneous dehydration of ethanol and ammonia, using alumina catalyst and temperatures of the order 300° to 400° C.

Kindler and co-workers (71) have noted the formation of benzyl phenethylamine by the alkylation of phenethylamine with benzyl alcohol in the presence of palladium catalyst.

Adkins and co-workers have described the alkylation of non-aromatic primary and secondary amines with alcohols by the use of copper-chromium oxide catalyst (84, 107, 124) and nickel catalysts (5, 124, 142). Bain and Pollard (9, 10, 11) have applied this method, using the former catalyst, to the preparation of piperazine derivatives from amines and amino-alcohols. For example, diethanolamine yielded N,N'-bis-(β-hydroxyethyl)-piperazine:

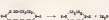


$$HOCH_2CH_2N\begin{matrix}CH_2CH_2{-}OH\ H\\ H\ HO{-}CH_2CH_2\end{matrix}NCH_2CH_2OH \longrightarrow HOCH_2CH_2N\begin{matrix}CH_2CH_2\\ CH_2CH_2\end{matrix}NCH_2CH_2OH$$

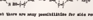
B. Discussion

It appeared that the application of the catalytic method of alkylating amines with alcohols to the synthesis of piperazine should result in a new and useful method of synthesizing this long-known compound. Though many methods are now known, almost all of them are impractical for commercial production. Even those methods which are possible to carry out on commercial scale have numerous disadvantages.

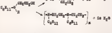
The piperazines previously prepared by the method under consideration were synthesized from amines and amino-alcohols. In the case of each ring closure, two molecules were involved, and two molecules of water were split out. Either a diethanolamine reacted with a primary amine,



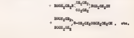
or two molecules of the ethanolamine type reacted to form a piperazine ring, with splitting of two molecules of water,



It is evident that there are many possibilities for side reaction. This tendency is reduced; and there remains only the possibility of linear polymer formation as a side reaction when the nitrogen atom already is partially substituted, as is the reaction in which N-cyclohexylethanolamine formed 1,4-dicyclohexylpiperazine:



However, when the dehydration reaction is applied to the synthesis of piperazine itself, it is apparent that numerous side reactions are possible in the case of bimolecular reaction, leading to linear and branched-chain polymers.

1. 

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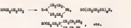
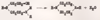


The first reaction is not feasible for the additional reason that ammonia is less reactive toward alkylation than is a primary or secondary amine.

It is apparent that side reaction can be minimized by carrying out an intramolecular dehydration, in which only one molecule of water is removed per molecule of piperazine formed:



The indicated starting material, N-(β-hydroxyethyl) ethane diamine, is commercially available (Carbide and Carbon). From the standpoint of availability, it is a particularly attractive starting material. While there has been no great technical demand for this compound, it is available in considerable amounts as a by-product, formed during the manufacture of ethane diamine, diethene triamine, and other polyethene polyamines. Should this source provide inadequate amounts it readily can be synthesized, as is pointed out in the Introduction, by alkylating ethane diamine with ethene oxide. Ethane diamine is available in high yield from the ethene-chloride-ammonia reaction, and large amounts are available as a by-product in the manufacture of ethene chlorohydrin.

By maintaining a high concentration of ethane diamine, high yields of hydroxyethyl ethane diamine may be obtained from the reaction with ethene oxide. This reaction, which will be discussed in Part C, was investigated by Knorr and Brownsdon (76) and is of considerable interest in comparing the respective availabilities of hydroxyethyl ethene diamine and diethene triamine as starting materials for the synthesis of piperazine. Diethene triamine cannot be prepared in essentially 100% yield by any reaction or series of reactions; but it is formed concurrently with ethene diamine and the whole series of polyethene polyamines.

4. Experimental

Equipment.--In the present investigation on the synthesis of piperazine two series of experiments were carried out, both sets of experiments being liquid-phase reactions. The first series was carried out in an autoclave under superatmospheric pressure. The autoclave used was an American Instrument Company hydrogenation bomb of 750 ml. capacity, electrically heated and provided with a shaker for agitation.

The reaction mixtures were fractionated by distillation through a fifteen-inch column packed with glass Raschig rings and provided with a Hopkins type condenser. The condenser was designed for the distillation of solids, being fitted to the distillation head by a standard taper connection. Thus it could be removed from the head when it was desired to scrape off any adhering piperazine. The condenser was provided with an off-set drip-point, so that the amount of reflux could be regulated a certain amount by rotating the condenser in its standard taper connection.

The second series of experiments was carried out at atmospheric pressure in a reaction flask, in some cases using an admixed solvent for a diluent. The flask was fitted with the above-described distillation column, and piperazine and water were continuously fractionated from the higher boiling reactant while the products were being formed.

The distillation column was provided with an electrically-heated jacket. In all cases the distillation flask or reaction flask was heated by an electrical heater which minimized bumping by even heat distribution on the lower hemispherical surface of the flask. This type of heating made it possible to avoid super-heating any of the contents of a distillation flask and minimized decomposition.

Experimental procedure.--The following two experiments are described in detail, to exemplify the experimental conditions used in the autoclave experiments.

Preparation of piperazine from N-(β-hydroxyethyl) ethane diamine, using Raney nickel catalyst.--65 grams of redistilled Carbide and Carbon hydroxyethyl ethane diamine, 400 ml. of purified dioxane, and between 10 and 15 grams of Raney nickel catalyst were charged into the autoclave. The Raney nickel was prepared from the Raney nickel alloy by the procedure of Covert and Adkins (44). The high heat was turned on, and when the temperature reached 187° (5:05 PM.), shaking was started. The temperature was maintained at 200° (±5°) for three hours (8:05 PM.), after which the heat was turned off and shaking was stopped. The next day the bomb was opened; there was a strong odor of ammonia. The solution was separated from catalyst by suction filtration; bomb and catalyst were rinsed with 25 ml. of dioxane, which was combined with the filtrate.

The solution was fractionally distilled through the short Raschig-ring packed distillation column. At the beginning of the distillation there was a tendency for the liquid to bump due to liberation of dissolved ammonia. The first dioxane boiled at 82°, separating into two phases due to presence of a few drops of heavier-than-water oil of unknown identity. The boiling point then rose to 87°, the boiling point of the dioxane-water azeotrope. When most of the water had distilled over in the azeotropic mixture, the boiling point gradually rose to 102-103°, when anhydrous dioxane distilled over. After 420 ml. of dioxane (including water) had been collected, the boiling point rapidly rose to about 140°. The receiver was changed and 36 grams of anhydrous piperazine was collected, boiling mainly between 140° and 150°. The residue was a viscous brown liquid. During distillation of the piperazine it was necessary to keep the piperazine melted as it flowed from the distillation head into the receiver because of the tendency of the product to solidify.

$$\text{Theoretical yield} = 85 \times \frac{86}{104} = 70 \text{ grams.}$$

$$\text{Percentage yield} = \frac{36}{70} \times 100 = 51.4\%$$

Preparation of piperazine using copper-chromium oxide catalyst.-- The autoclave was charged with 62 grams of N-(β-hydroxyethyl) ethylene diamine, 500 ml. of dioxane, 20 grams of copper-chromium oxide catalyst, and nitrogen gas under a pressure of 500 lbs. per sq. in. The catalyst was prepared according to the directions given by Adkins (8), using calcium nitrate and barium nitrate in the preparation as catalyst activators. The autoclave and contents were heated to 275° and shaken at this temperature for three hours. On cooling, the gas pressure was released; and the contents of the bomb was filtered from the catalyst.

The experiment was repeated three times, and the three combined portions were fractionated. After removal of dioxane-water and dioxane, the piperazine was collected as a white solid. The yield was 58 grams, forty-five per cent of the theoretical. The identity of the product was confirmed by preparing from it a sample of 1,4-dinitrosopiperazine, and taking a mixed melting point with an authentic sample of 1,4-dinitrosopiperazine.

Melting point: 156.3-157.0°

Melting Point of authentic sample: 157.0-158.0°

Melting Point, mixed: 156.0-157.4°.

It was established by the above experiments that the alkylation takes place, giving good yields of piperazine, when the alkylation catalysts utilized by Adkins and co-workers are used. These are Raney nickel and copper-chromium oxide. In order to study further the catalysts which are active in effecting this cyclization, similar experiments were carried out with various catalytic materials. The results of these experiments are summarized in Table I.

Catalysts used.--The preparation of Raney nickel catalyst and of copper-chromium oxide catalyst has been referred to above. Other catalysts which were tested were:

Activated alumina: a sample, "grade A, mesh 8-14", supplied by the Aluminum Ore Company.

Silica gel.

Fuller's earth

TABLE X

SYNTHESIS OF PIPERAZINE FROM N-(β-HYDROXYETHYL) ETHYLENE DIAMINE,

AUTOCLAVE METHOD

Page No.	Catalyst	Weight of Catalyst, grams	Weight of Reactant, grams	Vol. of Dioxane Diluent, ml.	Added Inert Atmosphere, lbs./sq. in.	Reaction Time (Hours)	Reaction Temp., °C.	Percentage Yield of Piperazine	Recovered Amine-alcohol, grams
45	Copper-Chromium Oxide	50	166	1050	800 lbs. N_2	5	275	46	—
57	Raney Nickel	10	58	400	----	5	200	31.4	0
57_2	Raney Nickel	30	156	1050	850 lbs. N_2	5	300	50	—
51	Activated Alumina	15	150	200	----	8	300	50	—
46	Silica gel	30	272	none	----	5	308	17.4	150
57	Fuller's Earth	28	130	300	----	3	300	5	51
75	Barium Oxide	38	150	300	----	3	300	0	123
49	Chromic Oxide	7	150	850	----	5	270-285	0	132
67	Cupric Oxide	30	163	300	----	5	275	45	—

TABLE I

(continued)

Page No.	Catalyst	Weight of Catalyst, grams	Weight of Reactant, grams	Vol. of Dioxane Diluent, ml.	Added Inert Atmosphere, lbs./sq. in.	Reaction Time (Hours)	Reaction Temp. °C.	Percentage Yield of Piperazine	Recovered Amino-alcohol, grams
69	Iron (Reduced by Hydrogen)	30	150	200	----	5	300	59.8	0
69	Palladium/Norit	5	150	200	----	6½	225-245	13	73
51	Platinum/Norit	5	150	200	----	9½	190-250	trace	---
66	Platinum/Asbestos; 5%	5	150	200	----	5	275	trace	110
73	Stannous Oxide	50	150	200	----	5	300	0 (?)	47
59	Norit	10	150	200	----	5	300	trace	91
71	Vermiculite	10	150	200	----	5	300	trace	90

Barium Oxide: Merck's pure grade, anhydrous

Chromic Oxide: prepared by decomposition of ammonium dichromate, Eimer and Amend C. P. grade, by careful heating.

Cupric Oxide: General Chemical Co.'s reagent grade.

Iron Reduced (by Hydrogen): Mallinckrodt U. S. P. grade.

Palladium/Norit: 10% palladium on norit "F", prepared by reduction of palladium chloride (8).

Platinum/norit: 5% platinum on norit "F".

Platinum/Asbestos: 5% platinized asbestos, Baker Chem. Co.

Stannous oxide: Eimer and Amend C. P. grade.

Norit: Grade "F" decolorizing charcoal, American Norit Co.

Vermiculite: the "exploded" variety.

From examination of the data in Table I, it is apparent that a wide variety of catalysts will function as dehydration catalysts in effecting cyclodehydration of N-(β-hydroxyethyl) ethane diamine. Materials which are most likely to show catalytic activity are the metals of group III, of group VIII and of sub-group B in groups I and II of the periodic table and their oxides, and the oxides of the elements below carbon in group IV of the periodic table. The catalysts preferably are used in a finely divided form and may be deposited upon a porous material such as activated charcoal.

Certain of the catalysts, including activated alumina and the activated oxides of silicon, titanium, zirconium and thorium, have maximum effectiveness when they have been prepared by special processes designed to yield catalytic materials. Often these catalysts contain a few per cent of combined water, such as "silica gel". These are well known as dehydration catalysts for other reactions, such as the preparation of ethers from alcohols. These catalysts are effective at a temperature of 300° or above. In the experiment with activated alumina (Table X), there was obtained a 20% yield of piperazine, and 54% of the starting material was recovered unchanged. This suggests that a maximum yield of approximately 40 to 44% may be expected. This yield is comparable with the yield obtained using cupric oxide at 275°, in which there was no unchanged starting material.

It can be noted that the other catalysts which gave fair yields of piperazine which are not dehydration catalysts, are all hydrogenation catalysts: copper-chromium oxide, Raney nickel, palladium on norit, iron (reduced), and cupric oxide. Platinum behaved anomalously in that it gave practically no piperazine. The catalysts of the hydrogenation type are effective at lower temperatures than are the catalysts of the dehydration type. Thus, the optimum use of Raney nickel is secured at 200° ; and copper-chromium oxide works well in the range 250° to 275°.

Effect of dilution.--Theoretically, it should be possible to secure 100 per cent yields of piperazine by using high dilution. Since the desired ring-closure is a monomolecular reaction, all reactions involving more molecules than one are side reactions and are undesirable when piperazine is the sought-after product. However, it is impractical to carry out the reaction under high dilution. In practice, a suitable amount of diluent dioxane is 200 ml. of dioxane per 150 grams of amino-alcohol.

The diluent should be water-absorbing, should be a good solvent for the reactant and product, and should be inert under the conditions of reaction. The diluent also serves to reduce the viscosity of the reaction mixture, aiding manipulation and filtration of the catalyst.

Dioxane has desirable properties as a diluent. Dioxane, with a boiling point of 101°, is readily separable from Piperazine, b. p. 146°, by fractional distillation. Dioxane also acts as a dehydrating agent during the distillation, forming an azeotrope of b. p. 87° which contains 20% water. Piperazine and water cannot be separated completely by distillation when distilled alone.

Slightly higher yields were obtained when a larger proportion of diluent was used. The highest yield, 51.6%, was obtained using a 17.8% solution of the amino-alcohol in dioxane and using Raney nickel as catalyst. However, the yield was not much lower in one experiment using a considerably more concentrated solution; with cupric oxide as catalyst, a 48% yield of piperazine was obtained. The dioxane solution used contained 43% of reactant. The maximum practical yield obtainable seems to be about fifty per cent.

Effect of pressure.--The liquid-phase catalytic alkylations of amines over hydrogenation catalysts generally have been carried out under hydrogen pressure of the order of 800 lbs. per sq. in., cold. However, it has been found[1] that satisfactory alkylations will take place when nitrogen gas is used in place of hydrogen. Nitrogen was used in two experiments of Table I. In the present investigation, it was found that an added gas pressure, such as that of hydrogen or nitrogen, is unnecessary. In one experiment in which no added nitrogen was used, the yield of piperazine was 51.4% of the theoretical. In a similar experiment with the same catalyst (Raney nickel) and using 500 lbs. per sq. in. (cold), the yield of piperazine was essentially the same, being 50% of the theoretical.

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[1] Unpublished data, Organic Chemistry Laboratories of the Univ. of Fla.

It appeared that it should be possible to effect this cyclization under conditions of atmospheric pressure, either by using a solvent which would provide a desired temperature of reflux, or without solvent. The reactant, N-(β-hydroxyethyl) ethane diamine, has a boiling point of 238°; this should be a suitable reaction temperature for some catalysts. Accordingly, the experiments listed in Table II were carried out.

TABLE II

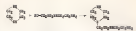
ALKYLATION AT ATMOSPHERIC PRESSURE

Exp. No.	Catalyst	Weight of Catalyst (Grams)	Weight of Amine-alco-hol (Grams)	Diluent and Weight (Grams)	Reaction Time (Hours)	Percentage Yield of Piperazine
1.	Raney nickel	6	160	---	6½	32
2.	Raney nickel	6	160	Diethyl Carbitol, 150	12	34
3.	Silica gel	10	115	---	10	24

A considerably longer reaction time was required for experiment No. 2 than for experiment No. 1, twelve hours in the one, and two and one-half hours in the other experiment. Since the same catalyst was used in both cases, this difference is due to the lower reaction temperature in No. 2. The reactions were carried out by refluxing the reaction mixtures with the catalyst; and the approximate initial reaction temperature for experiment No. 1 was the boiling point of N-(β-hydroxyethyl) ethane diamine, 238°. However, in reaction No. 2, diethyl carbitol of b. p. 188° was used as a diluent. This lowered the temperature of reflux. In each case the temperature of the reaction mixture would slowly rise as condensation of the amine-alcohol took place, forming products of higher molecular weights.

The yields of piperazine were somewhat lower than was the case in the autoclave experiments. The securing of maximum yields would require careful control; this is a problem of equipment design and of production. The aim of this series of experiments was to ascertain whether or not the cyclization would take place at atmospheric pressure.

A novel feature of this series of experiments was that the water and piperazine formed by the desired reaction were removed as formed by a process of continuous fractionation. When working under optimum conditions, this should prove advantageous, since it reduces the extent to which one of the theoretically possible side reactions can take place. The yield of piperazine can be reduced by alkylation of piperazine molecules with unreacted molecules of the amine-alcohol:


NH
CH$_2$
CH$_2$
CH$_2$
CH$_2$
NH
+ HO-CH$_2$CH$_2$NHCH$_2$CH$_2$NH$_2$
NH
CH$_2$
CH$_2$
CH$_2$
CH$_2$
N
CH$_2$CH$_2$NHCH$_2$CH$_2$NH$_2$

Another undesirable side reaction which may occur when water remains present is the hydrolysis of the carbon-nitrogen bonds of the amines present:

$$R\text{-}NH\text{-}R + H_2O \longrightarrow RNH_2 + R\text{-}OH$$

It has been demonstrated (11) that such a reaction sometimes takes place under alkylation conditions.

The details of procedure of the experiments summarized in Table II are exemplified by the description which follows of experiment No. 1 of this table.

Preparation of piperazine at atmospheric pressure.--160 grams of N-(β-hydroxyethyl) ethane diamine was refluxed with 5 grams of Raney nickel catalyst under a short distillation column. A strong odor of ammonia was evolved; and water distilled over. Soon a clear yellow distillate of b. p. 125° was collected at the rate of about 1 ml. per minute; and some piperazine solidified in the upper part of the condenser. The distillation was interrupted after 2½ hours, when 57 grams of distillate had been collected. 75 grams of tarry black residue remained in the distillation flask. By diluting the distillate to 500 ml. and titrating a 50 ml. portion with 0.1 normal acid (bromphenol blue indicator) it was found that 0.51 equivalent of base was present in the distillate. Assuming all the base present to be piperazine, this represented a 32% yield of piperazine.

Another 50 ml. aliquot was benzoylated by treatment with 10 grams of sodium hydroxide and adding with stirring 20 grams of benzoyl chloride dissolved in some dioxane. After two recrystallizations from ethanol, the product has a melting point of 191.7-192.8°. The melting point of an authentic sample of 1,4-dibenzoylpiperazine was 192.1-193.0°; mixed m. p., 191.7-193.0°. Part of the product was a chalky precipitate which did not dissolve readily in ethanol. This probably was a benzoyl derivative of some of the starting material present in the piperazine as an impurity.

Conclusions.--Piperazine may be synthesized in fifty per cent yield by agitating fifteen parts of N-(β-hydroxyethyl) ethane diamine dissolved in twenty parts of diluent dioxane with one part of Raney nickel catalyst, for three hours at a temperature of 200°. After filtration of the reaction mixture from the catalyst, pure anhydrous piperazine readily is obtained by fractional distillation.

Other catalysts may be used; but Raney nickel probably is most satisfactory.

The reaction may be carried out at atmospheric pressure by modifying the conditions; such a process gives satisfactory yields of piperazine when carried out in suitably designed equipment.

6. Summary

A process is described for the economic production of piperazine from N-(β-hydroxyethyl) ethene diamine, a readily available starting material. The present process is a distinct advance in the art, and its commercial application should make piperazine a tonnage chemical on the market.

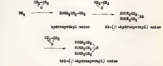
Two embodiments of the process are discussed, the one an autoclave method and the other a reaction at atmospheric pressure.

Uses of piperazine are discussed; and a review of the development of methods of piperazine synthesis is given.

B. The Reaction of Piperazine with Ethene Oxides

1. Review of the Literature

The reaction of an ethene oxide with ammonia or with an amine, a reaction of great interest in synthetic organic chemistry, was investigated by Knorr (74) in 1897. The reaction yields 1,2-amino-alcohols; and Knorr obtained a mixture of mono-, di- and tri-hydroxyethyl amines by treating aqueous ammonia with ethene oxide:

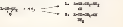

hydroxyethyl amine

di-(β-hydroxyethyl) amine

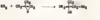
tri-(β-hydroxyethyl) amine

An interesting feature of the reaction was that the three products readily could be separated by fractional distillation. By using a large excess of ammonia, the primary amine was obtained as the main product.

An unsymmetrically substituted ethene oxide would appear to be capable of reacting in either of two ways, according as which carbon atom remains linked to the oxygen atom:

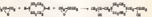


It was ascertained by Krassuski (77) that the reaction proceeds as in case 1. According to the rule of Krassuski, an asymmetrically-substituted 1,2-oxide combines with ammonia to form amino-alcohols in which the hydroxyl is attached to the carbon atom which, in the original compound, was associated with the least number of hydrogen atoms. The reaction of ammonia with 2,2-dimethylethane oxide to yield 2-hydroxy-2-methylpropylamine exemplifies this rule:

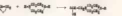


The secondary amine is formed at the same time.

The reactions of certain ethane oxides with piperazine have been investigated. In 1939 Krassuski and Kosenko (78) carried out reactions of piperazine with the oxides of 2,2-dimethylethane and trimethylethane. Hammer (80) obtained an amino-alcohol from piperazine and isosafrole oxide. Krassuski and Pilyagin (79) interreacted piperazine and propene oxide, obtaining the disubstituted product 1,4-bis-(β-hydroxyethyl)piperazine,



In all of these investigations, only disubstituted piperazines were isolated. It appeared that mono-substitution should be possible:



Failing to isolate a mono-substituted product, Krassuski and Kosenko, the initial investigators, concluded that the reaction proceeds with simultaneous addition of two molecules of alkene oxide to one molecule of piperazine, thereby yielding only disubstituted product.

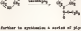
However, Fourneau and Barrelet (83) soon disproved this hypothesis, in part at least, by obtaining both mono- and dialkylated piperazines from the reaction of piperazine with the oxides of 3-methylbutene-1, 3-butoxypropene-1, 3-phenylpropene-1, and 3-phenoxypropene-1. A French patent (130) has been granted on this series of compounds.

Certain of the substituted piperazines prepared by Fourneau and Barrelet were effective as local anesthetics. In a further search for compounds with local anesthetic properties Fourneau and Ramdahl (84) prepared two series of disubstituted piperazines, utilizing ethene oxides as alkylating agents. One series utilized oxides of the type $RC(CH_3)CH_2O$, with R extending from propyl through heptyl; the other series was derived from 3-alkoxypropene-1 oxides, $ROCH_2CHCH_2O$, the alkoxy groups ranging from propoxy through heptoxy.

Adelson, MacDowell and Pollard (4) have obtained 1,4-bis-(β-hydroxyethyl)piperazine from the reaction of piperazine with ethene oxide.

Mousseron (129) has synthesized the series of mono- and disubstituted piperazines derived from the oxides of cyclopentene, cyclohexene, cycloheptene, cycloöctene, and indene.

It is evident that the alkylation of piperazine with an ethene oxide is of great importance as a method of obtaining mono-substituted piperazine derivatives. These have been difficult to prepare. An example of mono-substitution of piperazine was the synthesis by Moore, Boyle and Thorn (99) of ethyl piperazine-carboxylate by treatment of aqueous piperazine with ethyl chlorocarbonate. By adjusting the pH of the solution to the neutral point of bromophenol blue, it was possible to obtain a small yield of mono-substituted product:



This was used further to synthesize a series of piperazines substituted only in the 1-position. However, when piperazine ordinarily is treated with reagents such as halo-compounds, the mono-substituted piperazine formed as an intermediate is considerably more reactive than piperazine itself, and only 1,4-disubstituted piperazine can be isolated from the reaction mixture. In the case of reaction with ethyl chlorocarbonate, only disubstituted product is obtained when the pH of the piperazine solution has not been adjusted properly.

Other N-mono-substituted piperazines have been synthesized by ring closures which yielded 1-substituted piperazines. Outstanding was the synthesis of 1-phenylpiperazine from aniline and diethanolamine by Pollard and MacDowell (118).

2. Discussion

This phase of the present investigation resolves into the following objectives:

1. To utilize alkylation by means of ethene oxide as a means of

synthesizing 1-(β-hydroxyethyl)piperazine.

2. To synthesize 1-(β-hydroxypropyl)piperazine, which Krasuskii and Pilyugin failed to obtain in their investigation of the piperazine-propene oxide reaction.

3. To synthesize 1-(β-hydroxy-β-methylpropyl)piperazine, which Krasuskii and Kosenko concluded was not formed in the reaction of piperazine with 2-methylpropene oxide.

4. To demonstrate that the extent of mono-alkylation of piperazine by means of ethene oxides depends upon the molar ratio of piperazine used, and that an ethene oxide alkylation does not proceed preferentially with the mono-substituted derivative when unreacted piperazine is present.

5. To demonstrate that mono-alkylation of piperazine by means of ethene oxides is feasible with the more reactive oxides, the oxides of ethene and propene, as well as with the higher-molecular weight oxides used by previous investigators.

Experimental procedure.--The alkene oxide was added to a methanol solution of piperazine at a suitable temperature, was ranging from 35° to 50°. Knorr (73) found that ammonia and ethene oxide are unreactive when mixed in pure, anhydrous condition; but smooth reaction took place in the presence of water. Alcohols may be used as reaction medium; methanol is satisfactory. In some cases, only sufficient methanol was used to dissolve the piperazine.

The reaction mixtures were allowed to stand for some hours; and the methanol was removed by distillation at atmospheric pressure. The pure monosubstituted piperazine then was obtained by fractional distillation at reduced pressure.

3. 1-(β-Hydroxyethyl)piperazine

Ethene oxide reaction, No. 1.—198 grams (2.3 moles) of piperazine was dissolved in 3 L. methanol and placed in a flask provided with a reflux condenser and an inlet tube. External cooling was provided by means of a water bath. A bottle containing 100 grams (2.3 moles) of ethene oxide was connected to the inlet tube by rubber tubing; and the ethene oxide (b. p. 10.75°) was caused to distill into the flask by immersing the bottle in a beaker of water kept warm over a low gas flame. The reaction was carried out at such a rate that the temperature in the flask remained in the range 30° to 40°. The reaction readily was controlled by regulating the rate of distillation of ethene oxide.

The mixture was separated into its components by fractional distillation. After distillation of the methanol approximately 84 grams of piperazine was collected. The residual yellow oil was distilled at reduced pressure (Table III).

TABLE III

PIPERAZINE-ETHENE OXIDE REACTION

Fraction No.	Boiling Point	Weight, grams	Cumulative Weight
1.	121°/13 mm.	5.2	5.2
2.	121-123°/10 mm.	98.8	104.0
3.	123-128°/10 mm.	3.0	107.0

The 78 grams of solid residue was 1,4-bis-(β-hydroxyethyl)piperazine.

Yields, crude:

Piperazine (recovery):	54 g.,		37%
1-(β-Hydroxyethyl)piperazine:	107 g.,	0.82 mole,	38%
1,4-bis-(β-Hydroxyethyl)piperazine:	78 g.	0.45 mole,	40%,

based upon ethene oxide.

Ethene oxide reaction, No. 5.--A procedure similar to the above was used, except that there was an excess of piperazine. 1200 grams (14 moles) of piperazine dissolved in 1 L. of warm methanol was reacted at 80° with 220 grams (5 moles) of ethene oxide. The piperazine recovery was 844 grams (9.8 moles). The recovery of pure 1-(β-hydroxyethyl)piperazine by fractional distillation is summarized in Table IV.

TABLE IV.

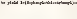
PIPERAZINE-ETHENE OXIDE REACTION

Fraction No.	Boiling Point	Index of Refraction	Weight	Cumulative Weight
	°C./10 mm.	$n_D^{29.5}$	grams	grams
1.	Up to 117	1.4867	15	15
2.	117-118.5	1.5005	40	55
3.	118.5-120.5	1.5021	207	262
4.	120.6	1.5028	227	487
5.	120-137	1.5010	12	499
6.	Residue		104	

Yields:

Piperazine (Recovery):	544 grams,	6.3 moles;	45%
1-(β-Hydroxyethyl)piperazine,	499 grams,	3.8 moles;	70%
1,4-bis-(β-Hydroxyethyl)piperazine:	104 grams,	0.6 mole;	24%.

Characterization: preparation of the phenyl thiourea of 1-(β-hydroxyethyl)piperazine.--1-hydroxyethylpiperazine contains one replaceable amino hydrogen; and it reacts with a molar quantity of phenyl isothiocyanate to yield 1-(N-phenyl-thiocarbamyl)-4-(β-hydroxyethyl)-piperazine,



13 grams of phenyl isothiocyanate was mixed with 13 grams of 1-(β-hydroxyethyl)piperazine, forming a homogeneous yellow oil. Heat was evolved. On cooling, an amorphous mass similar to resin was obtained. This was dissolved in hot absolute ethanol. The white crystalline product separated from the cooled solution after seeding with crystals obtained by placing a small amount of a heptane-absolute ethanol solution of the crude produce in the ice chest. The product, recrystallized from ethanol, had a melting point of 114.8-115.8° (corr.).

Dihydrochloride of 1-(β-hydroxyethyl)piperazine.--The dihydrochloride was prepared by adding excess dilute hydrochloric acid (bromphenol blue indicator) to the amine, evaporating to a syrup on the water-bath, cooling, and precipitating by addition of absolute ethanol. The granular crystalline solid was filtered, washed on the filter with

95% ethanol, and recrystallized from aqueous alcohol. The product, after air-drying, was dried in vacuum over phosphorus pentoxide. The melting point was 188.6-189.6° (corr.); (lit., m. p. 182-183° (113)).

Analysis (gravimetric as AgCl):

	Found	Calculated
Chlorine:	34.90%	34.91%

Picrate.--The picrate of 1-(β-hydroxyethyl)piperazine was prepared by mixing alcohol solutions of the amine-alcohol and of picric acid. After recrystallization from aqueous alcohol and drying in a vacuum over phosphorus pentoxide, it melted with decomposition at ca. 245° (corr.); at temperatures down to ca. 240°, it slowly decomposed without melting. Lit., m. p. 247-248° (112).

Summary of Properties of 1-(β-Hydroxyethyl)piperazine.

Physical State: light yellow viscous liquid with a mild amine odor.

Empirical Formula: $C_6H_{14}N_2O$

Structural Formula:

$$HOCH_2CH_2-N\begin{matrix} CH_2-CH_2 \\ CH_2-CH_2 \end{matrix}N-H$$

Molecular Weight: 130.19

Boiling Point: 119.2°/10 mm. (corr.)

Density: $D_4^{20} = 1.0688$; $D_4^{28} = 1.0641$

Refractive Index: $n_D^{22} = 1.5069$; $n_D^{25} = 1.5055$; $n_D^{34.6} = 1.5026$

$$\Delta n / \Delta t = 0.00034 / {}^\circ C.$$

Summary of Derivatives of 1-(β-Hydroxyethyl)piperazine.

Phenylthiourea: m. p. 118.9-118.3° (corr.)

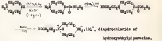
Dihydrochloride: m. p. 188.6-189.6° (corr.) (lit. 182-183° (119)).

Picrate: m. p. 245° (dec.) (lit., m. p. 247-248° (113)).

Chloroplatinate: dec. 248° (lit. (113)).

A procedure is described for the preparation in good yield of 1-(β-hydroxyethyl)piperazine, making this interesting mono-substituted piperazine readily available. It is noteworthy that previous investigators have obtained this amino-alcohol in small yield by tedious synthetic methods. It has not been completely described heretofore.

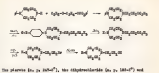
It was obtained by Moore, Boyle and Thorn (99) by the following synthetic route:



dihydrochloride of hydroxyethylpiperazine.

These investigators prepared the dihydrochloride, the chloroplatinate, and the chloroaurate; but melting points are not given.

Prelog and co-workers obtained the amino-alcohol by the following steps:



The picrate (m. p. 267-8°), the dihydrochloride (m. p. 182-3°) and the chloroplatinate (d. 248°) were reported.

In conclusion, it can be stated that the present investigation provides a method of synthesizing this almost unknown compound by a reaction which is easily carried out, which uses easily available starting materials, and which gives a high yield of product.

The by-product of this reaction, 1,4-bis-(β-hydroxyethyl)-piperazine, has been prepared previously (4) by the piperazine-ethene oxide reaction. The melting point after recrystallization from absolute ethanol was 134.5-135.0° (corr.). (Lit., m. p. 134-136° (116)).

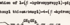
4. 1-(β-Hydroxypropyl)piperazine

Propene oxide reaction.--This reaction was carried out in a manner analogous to the experiment with ethene oxide on page 36. 232.4 grams (4.1 moles) of propene oxide was added by means of a dropping funnel to the piperazine (352.5 grams, 4.1 moles) dissolved in 2 L. methanol. 86 grams (1 mole) of piperazine was recovered from the reaction mixture by distillation. The yield of 1-(β-hydroxypropyl)-

piperazine, b. p. 107.8° (corr.) at 10 mm., was 260 grams (1.8 moles), a yield of 44%.

The residue, 226 grams (1.12 moles) of crude 1,4-bis-(β-hydroxypropyl)-piperazine, was the product obtained by Krasuskii and Pilyugin (78) by the alkylation of piperazine with propene oxide. The melting point of the white crystals obtained by recrystallization from hexane-absolute alcohol was 116.7-117.2° (corr.); lit., 115-116° (78). The picrate, recrystallized from aqueous alcohol, m.p. ca. 256° (dec.) (corr.); lit., m. p. 228-30° (78). The dihydrochloride was prepared in the manner described on page 38; m. p. 223.7-224.7° (dec.) (corr.).

Characterization of 1-(β-hydroxypropyl)-piperazine.--The phenyl thiourea, 1-(N-phenyl thiocarbonyl)-4-(β-hydroxypropyl)-piperazine,



was prepared by essentially the same procedure followed in preparing the hydroxyethyl derivative (page 38). The melting point of the soft white leaf-like crystals was 144.0-144.8° (corr.).

Dihydrochloride of 1-(β-hydroxypropyl)-piperazine.--1-(β-hydroxypropyl)-piperazonium chloride was prepared by the procedure outlined on page 38; the melting point was ca. 237.2° (dec.) (corr.).

Analysis (gravimetric as AgCl):

	Found	Calculated
Chlorine	32.58%	32.66%

Picrate (procedure, page 39): m. p. 174.6-177.6° (corr.)

Summary of Properties of 1-(β-Hydroxypropyl)-piperazine.

Physical State: light yellow viscous liquid with a mild amine odor.

Empirical Formula: $C_7H_{16}N_2O$

Structural Formula:

$CH_3-\underset{OH}{CH}-CH_2-N\begin{matrix}CH_2CH_2\\ \\ CH_2CH_2\end{matrix}N-H$

Molecular Weight: 144.22

Boiling Point: 108.3°/10 mm. (corr.)

Density: $d_4^{20} = 1.0108$

Refractive Index: $n_D^{22} = 1.4911$; $n_D^{29} = 1.4877$

$$\Delta n/\Delta t = 0.0006/\ ^\circ C.$$

Summary of Derivatives of 1-(β-Hydroxypropyl)-piperazine.

Phenylthiourea: m. p. 144.0-144.8° (corr.)

Dihydrochloride: m. p. ca. 237.2° (corr.)

Picrate: m. p. 176.5-177.5° (dec.) (corr.).

This method, then, affords a satisfactory method for the preparation of the hitherto unknown 1-(β-hydroxypropyl)-piperazine. It is shown that the propene oxide-piperazine reaction readily may yield this mono-substituted piperazine, as well as the disubstituted product obtained previously by Krasuskii and Pilyugin (79). It is unnecessary to carry out the reaction in a sealed tube, as was done by these authors. The yield of mono- plus disubstituted product was practically theoretical, based upon the amount of propene oxide used.

B. 1-(β-Hydroxy-β-methylpropyl)-piperazine.

2-Methylpropene-1 oxide reaction.--430 Grams (4 moles) of piperazine was hotted with 200 ml. of methanol until it was completely dissolved; 216 grams (3 moles) of 2-methylpropene-1 oxide (isobutylene oxide) slowly was added to the hot solution (78-80°) with frequent shaking. The methanol was distilled off; the piperazine and the two solid products were separated by distillation and redistillation through a fractionating column. The following fractions were collected during the first distillation:

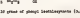
1. B. p. up to 145°, 177 grams.
2. B. p. 145-175°, 24 grams.
3. B. p. 175-217°, 28 grams.
4. Residue, 400 grams.

Fraction 1. was redistilled; after collecting 147 grams as piperazine, No. 2 and No. 3 were added. The lower boiling portion then was collected as crude piperazine. The residue was added to No. 4; and distillation was carried on at reduced pressure. 302 grams of white crystalline solid, m. p. 71-77°, needles, was collected at 105-110° at a pressure of approximately 12 mm. The distillation residue, 111 grams, had a m. p. of 97-102°. The mixed m. p. of distillate and residue was 61-76°.

The distillate, 302 grams (1.92 moles) of crude 1-(β-hydroxy-β-methylpropyl)-piperazine, was recrystallized from hexane. The melting point of the recrystallized product after drying in a vacuum desiccator over potassium hydroxide was 79.7-80.5° (corr.). A sample recrystallized a second time had a melting point of 80.2-80.8° (corr.).

The residue, 111 grams (0.48 mole) of crude 1,4-bis-(β-hydroxy-β-methylpropyl)-piperazine, was the product obtained by Krasuskii and Kosenko (78) by the action of isobutylene oxide on piperazine. The melting point of a sample recrystallized from hexane-absolute alcohol was 101.5-102.5° (corr.) (lit., 102-102.5° (78)).

Characterization of 1-(β-hydroxy-β-methylpropyl)-piperazine.-- The phenylthiourea, 1-(N-phenyl thiocarbamyl)-4-(β-hydroxy-β-methylpropyl)-piperazine,



was prepared by adding 10 grams of phenyl isothiocyanate (0.074 mole) to a slight excess (12.6 grams, 0.08 mole) of 1-(β-hydroxy-β-methylpropyl)-piperazine dissolved in 50 ml. of warm absolute alcohol. The solution was heated for several minutes. On cooling, cocoon-like tufts of furry crystals separated out. The melting point of the dry product was 129.5-129.8° (corr.). After recrystallization from absolute alcohol and drying in vacuum over phosphorus pentoxide, the melting point was 129.5-129.8° (corr.).

The dihydrochloride and the picrate were prepared according to the procedures used previously(pages 58 and 59). The dihydrochloride decomposed without melting ca. 215°, and decomposed slowly at temperatures somewhat below 215°. Picrate, m. p. 237° (dec.) (corr.).

Summary of Properties of 1-(β-Hydroxy-β-methylpropyl)-piperazine.

Physical State: white crystals, needles or prisms, with a slight odor.

Empirical Formula: $C_8H_{18}N_2O$

Structural Formula:

$$HO-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-N\begin{matrix}CH_2CH_2\\ \\CH_2CH_2\end{matrix}N-H$$

Molecular Weight: 158.24

Boiling Point: 69.5°/3 mm. (corr.); 96.1°/6.4 mm. (corr.); 108.0°/10 mm. (corr.)

Melting Point: 60.2-60.5° (corr.)

Summary of Derivatives of 1-(β-Hydroxy-β-methylpropyl)-piperazine.

Phenylthiourea: m. p. 129.5-129.8° (corr.)

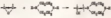
Dihydrochloride: dec. ca. 215°

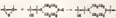
Picrate: m. p. 237° (dec.) (corr.)

The statement of Krasuskii and Kosenka (78) that the reaction of piperazine with isobutylene oxide does not yield a mono-alkylated piperazine has been disproven. This product has been obtained as well as the disubstituted product obtained by the above authors. It is unnecessary to carry out the reaction in a sealed tube; reaction proceeds readily at 75-80° in a methanol solution. The yield of the two products is almost the theoretical yield, based upon the weight of alkene oxide used.

6. Effect of Excess Piperazine

During reaction of an alkene oxide with piperazine, there are two competitive reactions.

1. 

2. 

A molecule of alkene oxide may react either with a molecule of piperazine or with a molecule of the mono-alkylated piperazine. The relative amounts of the products depends upon the relative rates of the two reactions. This in turn depends upon the relative concentrations of piperazine and mono-alkylated piperazine. Thus, by increasing the piperazine concentration, the probability of reaction of an alkene oxide molecule with a piperazine molecule is increased, and a larger proportion of mono-substituted piperazine to di-substituted piperazine will be present in the reaction mixture. When two moles of alkene oxide are caused to react with a molar quantity of piperazine, the di-substituted piperazine is obtained in essentially 100% yield (4), and no mono-substituted product is left in the reaction mixture.

Therefore, when the mono-substituted piperazine is the desired product, it is desirable to use an excess of piperazine. In the laboratory it is impractical to use a large excess of piperazine because of difficulty in handling the piperazine condensate while separating unreacted piperazine from the reaction mixture by fractional distillation.

Piperazine tends to solidify in the distillation head because of its high melting point, 106-8°. It does not tend to become supercooled before solidifying, as is the case with many solid amino-alcohols. However, the high melting point of piperazine should not be particularly disadvantageous in commercial practice, when there only would be the problem of design of suitable condensation apparatus.

A study of the effect of excess piperazine was made by examining the yields of products in the experiments carried out above. The experiments are outlined in Table V. Table VI gives some of the same data expressed in moles, rather than in grams, of reactants and products. From these data experimental yields were calculated (Table VII); and the ratios of yields of mono-substituted piperazines to disubstituted piperazines were calculated (Table VIII). The latter data are embodied in a graph (Figure I), examination of which indicates that the relation of the molar ratios of the two types of products to variation in molar ratios of the reactants used is a linear relation, practically. For the piperazine : alkene oxide ratio of 1 : 1 , the point on the graph is taken from experiment No. 2 rather than experiment No. 1 because in the latter experiment the measured yield of products adds up only to 78% Consequently it was assumed that the yield data in this experiment has less validity than does the yield data in the three succeeding experiments. In carrying out the last three experiments, larger amounts of reactants were used and experimental technique was improved; in these experiments the yields were essentially 100%.

By use of the graph (Figure 1) one may determine the yield of mono-alkylated piperazine which will be obtained by a piperazine-alkene oxide reaction using any ratio of piperazine to alkene oxide. Thus, if one desires 95% conversion of the alkene oxide to mono-alkylated piperazine, five moles of piperazine should be present in the reaction vessel per mole of alkene oxide which is added.

TABLE V

REACTIONS OF PIPERAZINE WITH ALKENE OXIDES

No.	Alkene Oxide Used	Weight of Alkene Oxide	Weight of Piperazine Used	Amount of Piperazine Recovered	Yield of Mono-Sub. Piperazine	Yield of di-Sub. Piperazine
1.	Ethene Oxide	104 g.	199 g.	84 g.	107 g.	78 g.
2.	Ethene Oxide	280 g.	1200	850	489	106
3.	Propene Oxide	233	355	83	260	97
4.	2-Methyl-Propene-1 Oxide	214	430	190	365	111

TABLE VI

REACTIONS OF PIPERAZINE WITH ALKENE OXIDES

(Expressed in Moles)

No.	Alkene Oxide Used	Moles of Piperazine Used	Moles of Alkene Oxide Used	Yield of Mono-Sub. Piperazine	Yield of di-Sub. Piperazine
				moles	moles
1.	Ethene Oxide	2.3	2.3	0.83	0.45
2.	Ethene Oxide	14.0	6.6	3.8	0.6
3.	Propene Oxide	4.1	4.1	1.8	1.14
4.	2-Methylpropene-1 Oxide	4.0	3.0	1.38	0.45

TABLE VII

REACTIONS OF PIPERAZINE WITH ALKENE OXIDES

Percentage Yields

Alkene Oxide Used	Moles of Alkene Oxide Used	Moles of Mono-Sub. Product Obtained	Moles of Di-Sub. Product Obtained	Total No. of Moles of Alkene Oxide Used in Forming Both Products	Total Percentage Yield Based on Weight of Alkene Oxide Used
1. Ethene Oxide	2.3	0.82	0.45	1.72	75%
2. Ethene Oxide	3.0	2.4	0.3	3.0	100%
3. Propene Oxide	4.1	1.8	1.12	4.04	98%
4. 2-Methylpropene-1 Oxide	3.0	1.92	0.48	2.88	96%

TABLE VIII

EFFECT OF EXCESS OF PIPERAZINE

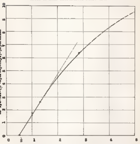
Alkene Oxide Used	Molar Ratio of Piperazine to Alkene Oxide	Molar Ratio of Mono-Substituted Piperazine to Di-Substituted Piperazine
1. Ethene Oxide	1 : 1	1.3 : 1
2. Ethene Oxide	3.3 : 1	3.3 : 1
3. Propene Oxide	1 : 1	1.3 : 1
4. 2-Methylpropene-1 Oxide	1.33 : 1	2.7 : 1

FIGURE I

PIPERAZINE-ALKENE OXIDE REACTION

Effect of Excess Piperazine Upon

Yield of Mono-Substituted Derivative



7. Summary

The reaction of piperazine with the oxides of ethene, propene, and 2-methyl-propene-1 (isobutylene) is described, with particular reference to the synthesis of mono-alkylated piperazines. Several new compounds are described and characterized. The effect of excess piperazine is discussed. The method affords a simple means of synthesizing several hitherto unknown or difficultly accessible compounds.

C. Mono-Alkylation of Ethene Diamine With Ethene Oxides

1. Foreword

In part A there was described a new method of piperazine synthesis which represents an improvement over the prior art in piperazine synthesis. This process has another interesting feature in that it is a general reaction which may be applied to the synthesis of carbon-substituted piperazines which formerly were difficult to prepare or were not available by other synthetic routes. This feature is discussed in the Introductino.

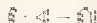
Inasmuch as the starting material for the synthesis of piperazine is N-(β-hydroxyethyl) ethene diamine,

$$H\text{-}N\begin{cases}CH_2CH_2\text{-}NH_2\\ CH_2CH_2\text{-}OH\end{cases}$$

the starting materials for the synthesis of substituted piperazines in general are substituted N-(β-hydroxyethyl) ethene diamines:

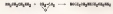
$$H\text{-}N\begin{cases}\overset{R}{\underset{R}{C}}-\overset{R}{\underset{R}{C}}-NH_2\\ \overset{R}{\underset{R}{C}}-\overset{R}{\underset{R}{C}}-OH\end{cases}$$

A series of these substituted amino-alcohols is available from ethene diamine itself through alkylation with ethene oxides



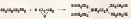
It is the purpose here to demonstrate that this reaction is entirely feasible and economical, as is postulated in the Introduction.

The reaction of ethene diamine with ethene oxide itself already has been described by Knorr and Brownsdon (76). Reaction was carried out in aqueous solution. By using an excess of ethene diamine--17 grams per 2.5 grams of the oxide--N-(β-hydroxyethyl) ethene diamine was obtained:



$$NH_2CH_2CH_2NH_2 + \underset{O}{CH_2-CH_2} \longrightarrow HOCH_2CH_2NHCH_2CH_2NH_2$$

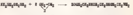
by using an excess of ethene oxide, N,N,N',N'-tetra-kis-(β-hydroxyethyl) ethene diamine was obtained:



$$NH_2CH_2CH_2NH_2 + 4\ \underset{O}{CH_2-CH_2} \longrightarrow \begin{matrix} HOCH_2CH_2 \\ HOCH_2CH_2 \end{matrix} NCH_2CH_2N \begin{matrix} CH_2CH_2OH \\ CH_2CH_2OH \end{matrix}$$

Sherlin, Berlin and Rabinovitch also have prepared the latter compound by this method (125).

MacDowell (81) has prepared N,N'-bis-(β-hydroxyethyl) ethene diamine by treating a methanol solution of anhydrous ethene diamine with ethene oxide:



$$NH_2CH_2CH_2NH_2 + 2\ \underset{O}{CH_2-CH_2} \longrightarrow HOCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$$

These reactions represent the total extent of the investigation of the reaction of ethene oxides with ethene diamines up to the present investigation.

It is apparent that mono-alkylation of ethene diamine is a reaction which is closely similar to mono-alkylation of piperazine. Ethene diamine and piperazine are related structurally:

NH_2
CH_2
CH_2
NH_2

Ethene Diamine

Piperazine

The two compounds are similar in their reactions as symmetrical 1,2-diamines. Consequently the mono-substitution of ethene diamine presents difficulties which are analogous to those encountered in the mono-substitution of piperazine. An investigation of the mono-alkylation of ethene diamine by ethene oxide, then, is a continuation of part B, The Reaction of Piperazine With Ethene Oxides.

Investigations upon mono-N-substitution of ethene diamine have been concerned mainly with acylations. Rosenmund (120) claimed a process for preparing monoacyl derivatives of ethene diamine by heating the diamine with an ester. Hill and Aspinall (68) described important extensions and improvements in this method; the ethyl ester of the organic acid was heated with anhydrous ethene diamine in a sealed tube at 100°. It is interesting to note that a patent has been granted to Bignamo (98) for a synthesis of monoacetyl ethene diamine from methylene aminoacetonitrile. The latter compound, on heating with acetic anhydride, yields methyleneacetylaminoacetonitrile, which gives monoacetylaminoacetonitrile on treatment with water. The product is obtained by hydrogenation:

$$CH_2=N-CH_2CN \xrightarrow[\Delta]{(CH_3CO)_2O} CH_2\left[N(COCH_3)CH_2CN\right]_2 \xrightarrow{H_2O} CH_3CONHCH_2CN$$

$$\xrightarrow{[H]} CH_3CO-NHCH_2CH_2NH_2$$

Monoacetyl ethane diamine is of value in the synthesis of other mono-substituted ethane diamines because of the ease of hydrolysis of the acetyl group. With the acetyl group protecting one of the amino groups, the other can be substituted. Thus Amundsen and Longley (7) prepared the mono-benzenesulfonyl derivative:

$$H_2NCH_2CH_2NH_2 \longrightarrow H_2NCH_2CH_2NH-COCH_3 \xrightarrow{\phi SO_2Cl} \phi SO_2-NHCH_2CH_2NH-COCH_3$$

$$\xrightarrow[HCl]{H_2O} \phi SO_2-NHCH_2CH_2NH_2$$

In a similar manner Moore, Boyle and Thorn (98) used the carbethoxy group to protect one of the amino groups of ethane diamine in order to obtain mono-substituted derivatives. Carbethoxy ethane diamine was prepared by treating with ethyl chlorocarbonate an acidified solution of ethane diamine, the pH being adjusted to the neutral point of bromcresol green[1].

$$H_2NCH_2CH_2NH_2 \quad ClCO_2C_2H_5 \qquad H_2NCH_2CH_2NH-COOC_2H_5$$

Bovet, de Lestrange and Fourneau (15) while investigating compounds of antispasmodic action prepared a series of N-mono-aryl ethane diamines.

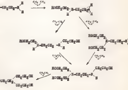
---

[1] Compare the preparation of carbethoxypiperazine by the same authors (p. 35).

2. Discussion

It is evident from the work of Knorr and Brownsdon, who prepared the simplest member of the series of compounds synthesized in this phase of this investigation, and from part B, which relates to the analogous reaction using piperazine, that optimum yields are to be obtained by using an excess of ethane diamine. From a technical standpoint, this is much easier to do than in the case of the piperazine reactions. Ethane diamine is a liquid of boiling point 116.5°, whereas piperazine is a solid of m. p. 105-6° and b. p. 145-6°. Therefore ethane diamine readily can be recycled.

Ethane diamine has four amino hydrogen atoms, while piperazine has two. Two concurrent reactions take place when ethane oxide is added to piperazine (p. 47) whereas a more complicated series of reactions occurs when ethane oxide is added to ethane diamine:



Because of the multiplicity of products it was not practical in the present series of reactions to attempt separation of the higher-boiling products.

Reactions were carried out with the oxides of propene, 2-methylpropene-1 (isobutylene), and phenylethene (styrene). The ethene diamine used was the aqueous Carbide and Carbon product with an ethene diamine content of 60 to 70%, which was purified by distillation. Methanol diluent was used in the case of phenylethene oxide. In the other experiments ethene diamine was the diluent. It was considered that the normal water content of the commercial ethene diamine was sufficient to catalyse the reaction.

The reaction mixtures were separated by fractional distillation. The distillation column was the Rauschig-ring packed column described on page 17.

5. N-(β-Hydroxypropyl) Ethene Diamine

Propene Oxide reaction No. 1.--342 grams (5.9 moles) of propene oxide was added slowly, with stirring, to 644 grams of 60.5% ethene diamine (6.48 moles) dissolved in 2 l. of methanol and contained in a 5-liter, 3-necked flask fitted with a reflux condenser. The temperature was kept at 40-50° by a water bath.

After the methanol was distilled off some white crystalline solid separated from the viscous yellow liquid. This had a melting point of 120-155° and melted at 140.5-142.5° after recrystallization from methanol. The ethene diamine was removed by distillation at reduced pressure, using a water pump. The recovered ethane diamine was 1.58 moles, determined by titration. The yield of N-(β -hydroxypropyl) ethane diamine, b. p. 112° at 10 mm. and 94° at 2 mm., was 284 grams (2.4 moles), a yield of 41%.

Propene Oxide reaction No. 2.--270 grams (4.65 moles) of propene oxide was added slowly with stirring to 2560 grams of hydrated ethane diamine (69.8%, 29.7 moles) at a temperature of 40-60°. The ethane diamine was removed by fractional distillation. 496 grams (4.2 moles) of amino-alcohol was collected by distillation at reduced pressure, a yield of 90.5%. The residue was 35 grams.

Characterization of N-(β -hydroxypropyl) ethane diamine.--The thiourea, the picrate and the dihydrochloride were prepared for characterization, using procedures described elsewhere (pp. 38 and 39).

The thiourea, N-(β -hydroxypropyl)-N,N'-bis-(N-phenyl thiocarbamyl) ethane diamine,

$$\begin{array}{l} \qquad\qquad\quad NH-\underset{S}{C}-NH\phi \\ \qquad\qquad\quad CH_2 \\ \qquad\qquad\quad CH_2 \\ CH_3\underset{OH}{CH}CH_2-N-\underset{S}{C}-NH\phi \end{array}$$

(from alcohol) had a melting point of 119.8-120.0° (corr.)

Picrate, m. p. 191.0-192.2°(corr.)

Dihydrochloride, m. p. 184.7-185.0 (corr.)

Analysis (gravimetric as AgCl):

	Found	Calculated
Chlorine:	37.18%	37.09%

Summary of Properties of N-(β-Hydroxypropyl) Ethane Diamine.

Physical State: water-white, slightly viscous liquid with a mild ammoniacal odor.

Empirical Formula: $C_5H_{14}N_2O$

Structural Formula: $\underset{\displaystyle OH}{CH_3-CH}-CH_2-NH-CH_2CH_2-NH_2$

Molecular Weight: 118.18

Boiling Point: 94°/3 mm. (corr.); 112°/10 mm. (corr.)

Density: $d_4^{25} = 0.9887$; $d_4^{25.0} = 0.9810$

Refractive Index: $n_D^{20} = 1.4758$; $n_D^{25} = 1.4725$; $n_D^{25.0} = 1.4726$

$\Delta n/\Delta t = 0.00040/°C.$

Analysis[1]:

	Found	Calculated
Nitrogen:	23.64%	23.69%

Summary of Derivatives of N-(β-Hydroxypropyl) Ethane Diamine.

Phenylthiourea: m. p. 149.8-150.0° (corr.)

Dihydrochloride: m. p. 184.7-185.0° (corr.)

Picrate: m. p. 181.5-182.5° (corr.)

---

[1] By titration with standard 0.1 normal alkali, using bromphenol blue indicator.

4. N-(β-Hydroxy-β-methylpropyl) Ethane Diamine

2-Methylpropene-1 Oxide Reaction.— The reaction was carried out in a 5 L., 3-necked flask provided with a thermometer well, reflux condenser and addition tube. 2718 grams of 70% ethane diamine (31.7 moles) was heated to 70°, and 365 grams (5 moles) of 2-methylpropene-1 oxide (isobutylene oxide) slowly was added, with constant shaking of the flask. The addition was at such a rate that the temperature remained in the range 70° to 80°. The ethane diamine was removed by distillation, in the main at atmospheric pressure and finally under vacuum with a water pump. 572 grams (4.33 moles) of pure product was collected at b. p. 105.7°/10 mm. and b. p. 81.2°/5 mm., a yield of 87%.

Characterization.--The picrate and dihydrochloride were prepared by the procedures described elsewhere (pp. 38 and 39). The phenyl thiourea, prepared by the usual procedure, was a glassy yellow solid which could not be obtained in crystalline state.

Analysis of dihydrochloride (gravimetric as AgCl):

	Found	Calculated
Chlorine:	34.62%	34.57%

Summary of Derivatives:

Picrate: m. p. 198.5-200.5° (dec.) (corr.)

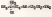
Dihydrochloride: m. p. 195.7-196.4° (corr.)

Summary of Properties of N-(β-hydroxy-β-methylpropyl) Ethane Diamine.

Physical State: water-white, slightly viscous liquid with a mild amine odor.

Empirical Formula: $C_6H_{16}N_2O$

Structural Formula:



$$CH_3-\underset{OH}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2-NH-CH_2CH_2-NH_2$$

Molecular Weight: 132.21

Boiling Point: 91.5°/8 mm.; 105.7°/16 mm. (corr.)

Density: $d_4^{25} = 0.9586$

Refractive Index: $n_D^{25} = 1.4672$ $n_D^{20} = 1.4685$

$\Delta n/\Delta t = 0.00026/ ^\circ C.$

Analysis (titration: bromphenol blue indicator):

	Found	Calculated
Nitrogen:	21.06%	21.18%

6. N-(β-Hydroxy-β-Phenylethyl) Ethane Diamine

Phenylethene Oxide Reaction.--270 grams (2.25 moles) of phenylethene oxide (styrene oxide) dissolved in 800 ml. of methanol was added slowly to a solution of 440 grams of ethane diamine (60.5%, 4.5 moles) in 500 ml. of methanol. The mixture was allowed to stand for several hours. The temperature gradually rose to the boiling point of methanol; and a white solid began to precipitate out after about an hour; 26 grams was filtered off. 246 grams of product (1.36 moles) was obtained by fractional distillation. The product, which boiled at approximately 186° at 10 mm., was a viscous yellow oil which solidified in the receiver while still out. After recrystallization from hexane-absolute alcohol, melted at 78-80°. 84 grams of residue was left in the distillation flask.

Characterization.--The dihydrochloride, recrystallized from alcohol and dried in vacuum over phosphorus pentoxide, melted at 198.7-200.8° (corr.)

Analysis of dihydrochloride (gravimetric as AgCl):

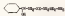
	Found	Calculated
Chlorine:	27.05%	28.01%

Summary of Properties of N-(β-Hydroxy-β-Phenylethyl) Ethane Diamine.

Physical State: white crystalline solid with a faintly amine-like odor reminiscent of oil of roses.

Empirical Formula: $C_{10}H_{16}N_2O$

Structural Formula:



$C_6H_5-\underset{OH}{CH}-CH_2-NH-CH_2CH_2-NH_2$

Molecular Weight: 180.25

Boiling Point: 184.8°/10 mm. (corr.)

Melting Point: 89.3-91.2° (corr)

6. N-(β-Hydroxyethyl) Ethane Diamine

The simplest member of this series of amino-alcohols, N-(β-hydroxyethyl) ethane diamine, has been synthesized previously (78).

It also is available commercially (Carbide and Carbon) as a by-product in the manufacture of polyethene polyamines. Nevertheless, it has not been well characterized. Therefore its properties are described here.

Characterization.—The picrate and dihydrochloride were prepared according to the usual procedure (pp. 38 and 39). The phenyl thiourea, prepared with phenyl isothiocyanate, was a glassy yellow solid which could not be crystallized.

Summary of Properties of Derivatives:

Picrate: m. p. 224° (dec.) (corr.)

Dihydrochloride: m. p. 114.3-115.2° (corr.)

Chloroplatinate: dec. 249° (lit. (76)).

Summary of Properties of N-(β-Hydroxyethyl) Ethene Diamine.

Physical State: light yellow, hygroscopic liquid of medium viscosity, with a mildly ammoniacal odor (23).

Empirical Formula: $C_4H_{12}N_2O$

Structural Formula: $HOCH_2CH_2$-NH-CH_2CH_2-NH_2

Molecular Weight: 104.15

Boiling Point: 238-240°/752 mm. (lit. (76)).

115.5°/6.2 mm.; 123°/10 mm. (corr.) (exp.)

Density: d_{20}^{20} = 1.0280-1.0330 (lit. (23))

d_4^{25} = 1.0254 (exp.)

Refractive Index: n_D^{25} = 1.4861

7. Discussion of Experimental Data

The experimental data of the syntheses outlined above are summarized in Table IX. From this data were calculated the percentage yields and the molar ratios of ethane diamine to alkene oxide used in the experiments (Table X). This ratio is an expression of the amount of ethane diamine in excess used in each experiment, the desired reaction requiring one mole of ethane diamine per mole of alkene oxide.

The relationship between percentage yield and excess of ethane diamine is expressed graphically from this data (Figure IX). The graph shows that yield of mono-alkylated ethane diamine may be expected from any given molar ratio of ethane diamine to alkene oxide which one may use. Thus, a 98% yield may be expected if one uses the ten-fold amount of ethane diamine; whereas if one uses the amount of diamine which is required theoretically, the yield of mono-alkylated product is only 45%.

TABLE IX

PREPARATION OF N-(β-HYDROXYALKYL) ETHANE DIAMINES

Exp. No.	Alkene Oxide Used	Amount of Alkene Oxide		Moles of Diamine present	Temp.	Yield of Product	
		grams	moles			grams	moles
1.	Propene Oxide	342	5.9	5.46	40-50°	284	2.4
2.	Propene Oxide	270	4.65	29.7	40-50°	496	4.2
3.	2-Methylpropene Oxide	365	5.0	31.7	70-80°	572	4.33
4.	2-Phenylethene Oxide	390	3.25	4.6	35-70°	246	1.36

TABLE X

PREPARATION OF N-(β-HYDROXYALKYL) ETHENE DIAMINES

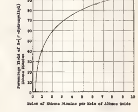
Yield Data

Exp. No.	Alkene Oxide Used	Molar Ratio of Ethene Diamine to Alkene Oxide	Percentage Yield
1.	Propene Oxide	6.62 : 1	41%
2.	Propene Oxide[1]	6.4 : 1	60.6%
3.	2-Methylpropene-1 Oxide	6.3 : 1	87%
4.	2-Phenylethene Oxide	2 : 1	60.8%

[1] The data for experiment No. 2 is not valid for computing Figure II; actually the molar ratio of ethene diamine to propene oxide in this experiment was somewhat higher than 6.4 : 1, for in this experiment a device was used by which ethene diamine distilled continuously into the reaction flask from a still pot and fractionating column; the reaction mixture overflowed continuously into the still pot from the reaction flask. The reaction product thus became more concentrated in the still pot than in the reaction flask.

FIGURE II

EFFECT OF EXCESS ETHENE DIAMINE IN THE REACTION OF ETHENE DIAMINE WITH ALKENE OXIDES



It is interesting to compare the proportion of N-β-hydroxyalkyl ethane diamines with the analogous piperazine derivatives. The boiling points of the two series of compounds derived from the oxides of ethene, propene and 2-methylpropene are given in Table XI.

TABLE XI

BOILING POINTS OF SOME N-SUBSTITUTED ETHANE DIAMINES AND PIPERAZINES

Substituent Group	Boiling Point/10 mm., N-Substituted Ethane Diamine	Boiling Point/10 mm., N-Substituted Piperazine
$HOCH_2CH_2$-	128°	119°
$HO\underset{CH_3}{CH}CH_2$-	112°	108.6°
$HO\overset{CH_3}{\underset{CH_3}{C}}-CH_2$-	103.7°	106.0°

8. Summary

The mono-alkylation of ethane diamine by reaction with alkene oxides is described. New compounds obtained by alkylation with oxides of propene, 2-methylpropene-1, and phenylethene are described and characterized. Hydroxyethyl ethane diamine is described and characterized more completely than it is described in the literature.

Methods of monosubstitution of ethane diamine are summarized; and the present method is compared with the analogous piperazine alkylation.

D. Application of the General Method to the Synthesis of C-Substituted Piperazines.

1. Summary of Previous Syntheses of C-Substituted Piperazines.

In Part A there was described a method for the synthesis of piperazine from N-(β-hydroxyethyl) ethene diamine, a starting material readily derived from ethene diamine and ethene oxide. In Part C there was outlined experimental work which indicates that the ethene diamine-alkene oxide reaction is useful for the synthesis of substituted amino-alcohols of the same type; these should yield substituted piperazines when subjected to the ring closure reaction which was found to yield piperazine in good yield. A further purpose of the experimental work of Part C was to prepare some of the hitherto unknown N-(β-hydroxyalkyl) ethene diamines for use as starting materials in the experiments described in the pages to follow.

Piperazines containing substituents on one or more of the carbon atoms have been synthesized by a number of the methods used for the synthesis of piperazine itself. The reactions are summarized:

1. Alkylation of an aryl sulfonamide with 1,2-dihalo compounds, and hydrolysis of the 1,4-diaryl sulfonyl piperazines obtained.--This reaction, the method of Markwald (p. 9), was utilized by Mach and Markwald (80) for the synthesis of 2-methylpiperazine. p-Toluene sulfonamide was treated first with propene dibromide, then with ethene dibromide. Wrede, Bruch and Keil (145) found the method unsatisfactory because of low yields, both when using benzene sulfonamide first with propene

dibromide, then with ethene dibromide and when first reacting the sulfonamide with ethene dibromide, then treating the intermediate $\phi SO_2N(Bz)-CH_2CH_2-N(Bz)SO_2\phi$ with propene dibromide.

2. Reduction of a 2,5-diketo piperazine.--The 2,5-diketopiperazines are available as the cyclic anhydrides or lactims of the amino-acids. Just as glycine anhydride yields piperazine (cf. p. 10), various other amino-acid anhydrides or mixed anhydrides yield substituted piperazines. Thus, 2-methylpiperazine, 2-isopropylpiperazine, 2-isobutylpiperazine, trans-2,5-dimethylpiperazine, 2,5-di-isobutylpiperazine, 2,5-di-(p-hydroxyphenylmethyl)-piperazine, 2-isopropyl-5-benzylpiperazine, 2-propyl-5-benzylpiperazine and 2-isopropyl-5-isobutylpiperazine have been prepared by the reduction of the anhydrides, respectively, of glycylalanine (2, 142), glycylvaline (142), leucylglycine (1), alanine (69), leucine (43), tyrosine (3), dl-valyl-dl-phenylalanine, dl-norvalyl-dl-phenylalanine, and dl-leucylvaline (144). Reduction has been effected by chemical means, using sodium and alcohol, by Cohn (40), by Moyer (69) and by Abderhalden and co-workers (1, 2, 3); while Wrede and co-workers (144, 143) have found electrolytic reduction effective.

3. Reduction of corresponding pyrazines.--By reduction with sodium and alcohol, 2-methylpiperazine (132), 2,5-dimethylpiperazine (133), 2,6-dimethylpiperazine (111), 2,5-di-isopropylpiperazine (43), 2,3,5-trimethylpiperazine (135), 2,5-dimethyl-3-ethylpiperazine (134), and 2,3,5,6-tetramethylpiperazine (143) have been synthesized from the corresponding pyrazines. Many of the pyrazines were obtained by Stoehr (132, 133, 134, 135, 122) by the reaction of glucose with aqueous ammonia at 100°

in a sealed tube; Pope and Read (111) used glycerine and aqueous ammonia.

The sodium and alcohol reduction of 2,5-dimethylpyrazine yielded mainly the trans- derivative, as well as some cis-2,5-dimethylpiperazine (73). Catalytic reduction over nickel yielded trans-2,5-dimethylpiperazine (61, 62).

Kipping (72) prepared four of the five theoretically possible 2,3,5,6-tetramethylpiperazines by using sodium and alcohol, aluminum amalgam, and tin with hydrochloric acid, as well as catalytic reduction over platinum. Each method of reduction yielded a different combination of mixed isomers.

5. Reduction of a dihydropyrazine.--A dihydropyrazine, obtained by condensation of an α,β-diketone with an α,β-diamine or by condensation of two molecules of an α-amino-ketone, readily may be reduced to the corresponding piperazine. Braunmüller (16, 32) obtained 2-methyl-3-propylpiperazine by condensing hexanedione-2,3 with ethene diamine and treating the product with sodium and alcohol. Similarly, Gabriel (56) reduced the 3,6-dihydropyrazine obtained by treatment of 3-amino-3-methyl-butanone-2 with alkali, obtaining the piperazine, 2,2,3,5,5,6-hexamethylpiperazine.

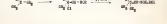
6. Reductive cyclization of an α-isonitroso-ketone.--Under reduction conditions, two molecules of an α-isonitroso-ketone alkylate each other to form a piperazine. Godchot and Mousseron (51, 52) hydrogenated an acetic acid solution of isonitroso-acetone, using platinum catalyst, and obtained a 70% yield of trans-2,5-dimethylpiperazine. Simi-

inely, isonitroso methyl ethyl ketone yielded isomeric 2,3,5,6-tetramethylpiperazines (61).

7. Reductive cyclization of α-hydroxy-acid amides.--According to Oeda (108) the catalytic hydrogenation of the amides of α-hydroxy-acids brings about alkylation between two molecules with formation of a piperazine. Thus lactamide, leucinamide, and phenyl-lactamide yielded, respectively, 2,5-dimethylpiperazine, 2,5-di-isobutylpiperazine, and 2,5-diphenylpiperazine.

8. Hydrolysis of an α,β-diacetamido compound.--When one of the acetamido groups of an α,β-diacetamido compound is attached to a tertiary carbon atom, the main product obtained upon removal of the acetyl groups by hydrolysis is a piperazine. Thus Reihlen and coworkers (117) obtained 2,2,5,5-tetramethyl piperazine by boiling α,β-diacetamido-β-methylpropane with conc. hydrochloric acid. Similarly α,β-diacetamido-β-phenylpropane yielded 2,5-diphenyl-2,5-dimethylpiperazine. The diacetamido- intermediates were derived from the corresponding α-acetamido nitriles by the Adams reduction, using acetic anhydride medium.

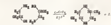
A variant of the above reaction was the reduction by Drew and Head (47) of α-aminoisobutyraldoxime hydrochloride to yield 2-methylpropane diamine (isobutylene diamine) and 2,2,5,5-tetramethylpiperazine. The intermediate was prepared from 2-methylpropene;



$$(CH_3)_2C=CH_2 \xrightarrow{NOCl} (CH_3)_2C(Cl)-CH=NOH \xrightarrow{NH_3/C_2H_5OH} (CH_3)_2C(NH_2)-CH=NOH.HCl$$

and the reduction was carried out with sodium amalgam-acetic acid.

9. Catalytic cyclo-dehydration of amino-alcohols.--The synthesis by Bain and Pollard (10) of trans-2,5-dimethylpiperazine by cyclo-dehydration of 2-hydroxypropylamine over copper-chromium oxide catalyst represents the nearest approach of known methods for the synthesis of C-substituted piperazines to the experimental work of the present investigation. The yield was 18%:



2. Synthesis of 2-Methylpiperazine

It readily may be seen from examination of the methods listed above that there previously have been no good general methods for the synthesis of C-substituted piperazines. The reduction of pyrazines gives good yields in some cases, but the pyrazines themselves are not readily available. On the other hand, piperazines which may be derived from N-hydroxyalkyl alkene diamines by the method described here may prove to be an improved source of certain substituted pyrazines, after methods of dehydrogenation of piperazines have been developed.

Satisfactory yields also have been obtained by electrolytic reduction of 2,5-diketopiperazines. However, the diketopiperazines are not readily available from economic sources. They are prepared in varying yields from β-amino-acids; these are, in general, expensive.

However, 2-methylpiperazine now has been prepared in a yield of

70.7%--based upon unrecovered starting material--from N-(β-hydroxypropyl) ethane diamine. The method followed was that outlined for the synthesis of piperazine itself (part A). The preparation of the starting material was described in part C.

It is interesting to compare the yields of 2-methylpiperazine obtained by various methods. These are listed in Table XII.

TABLE XII

METHODS OF SYNTHESIS OF 2-METHYLPIPERAZINE

Method	Percentage Yield	Investigators and Literature Reference
Sodium-Alcohol Reduction of 2-Methylpyrazine..........	(Not given)	Stoehr (132)
CH_3⬡$SO_2N(Na)CH_2\overset{CH_3}{CH}N(Na)SO_2$⬡$CH_3$ plus $BrCH_2CH_2Br$, then Hydrolysis.........	(Not given)	Bach and Marckwald (50)
$(\phi SO_2N(Na)CH_2)_2$ + $BrCH_2CH(CH_3)Br$, then Hydrolysis; or $\phi SO_2N(Na)CH_2\underset{CH_3}{CH}N(Na)SO_2\phi$ + $BrCH_2CH_2Br$, then Hydrolysis.........	Low yields; "unsatisfactory"	Wrede, Brush and Keil (145)
Sodium-Alcohol Reduction of Glycylalanine Anhydride, 2-Methyl-3,6-diketopiperazine..	28%	Abderhalden and Schwab (2)
Electrolytic Reduction of 2-Methyl-3,6-diketopiperazine............	48%	Wrede, Brush and Keil (145)
Ring Closure of N-(2-Hydroxypropyl) Ethane Diamine..................................	70.7%	Tables XIII and XIV

It may be noted that the maximum yield of 2-methylpiperazine obtained by any process used previously was 48%. This one obtained by electrolytic reduction of 2-methyl-3,6-diketopiperazine (148) using lead and lead dioxide electrodes and a two per cent solution of the diketopiperazine in 20% sulfuric acid.

Experimental.--The experimental procedure followed was the same as that followed in the preparation of piperazine (pp. 14 and 19). Experiments were carried out in the autoclave, using copper-chromium oxide and Raney nickel catalysts. The experimental conditions are outlined in Table XIII, and the yield data is summarized in Table XIV.

Raney nickel appears to be the preferred catalyst. By ring-closure using Raney nickel as catalyst, the yield of 2-methylpiperazine was 52.2%. Some starting material was recovered; the yield based upon unrecovered starting material was 70.7%. Therefore this reaction is a considerably better method for the preparation of 2-methylpiperazine than are previous methods from the standpoint of yield, as well as from standpoints of availability of starting material and ease of operation.

It is interesting to compare the yields of 2-methylpiperazine with the yields of piperazine obtained by the analogous reaction. It would appear that a higher yield of 2-methylpiperazine than of piperazine can be expected. It is well-known that the presence of alkyl substituents in a reactive molecule often facilitates ring-closure. According to Fuson (59), "It is a general rule that the presence of alkyl groups and particularly the gem-dimethyl grouping ($(CH_3)_2C$) enhances the tendency of a chain to undergo cyclization". The ring closure of a N-(β-hydroxyalkyl) ethane diamine seems to be in accordance with this rule. Under practical operating conditions the yield of piperazine, the unsubstituted member of the series, was about fifty-two per cent (Table I). The yield of 2-methylpiperazine which can be obtained under similar conditions seems to be considerably higher, about seventy per cent.

With reference to the application of the above rule to the closure of the piperazine ring, one should especially note the ring closures discussed in par. 2, p. 74. These seem to be examples of spontaneous ring closures of 1,N-diamines containing the gem-dimethyl grouping.

2-Methylpiperazine has been described in the literature, and it has been well-characterized. One additional derivative was prepared, the bis-phenyl thiourea. Recrystallized from benzene-absolute alcohol, the melting point was 189.0-189.5°(corr.). The properties of 2-methylpiperazine are listed below and in Table IV.

Properties of 2-Methylpiperazine.

Physical State: white crystalline solid, with a piperazine-like odor.

Empirical Formula: $C_5H_{12}N_2$

Structural Formula:

Molecular Weight:	100.17
Melting Point:	62° (60)
Boiling Point:	155°/758.1 mm. (60)
	155-155.5°/763 mm. (corr.) (122)

TABLE XXII

SYNTHESIS OF 2-METHYLPIPERAZINE FROM N-(β-HYDROXYPROPYL) ETHANE DIAMINE

Reaction Conditions

		Exp. No. 1		Exp. No. 2
Catalyst Used	:	Copper-Chromium Oxide	:	Raney Nickel
Weight of Catalyst	:	10 grams	:	10 grams/batch
Weight of N-(β-Hydroxypropyl)Ethane Diamine	:	58 grams (0.57 moles)	:	250 grams (2.28 moles) in two batches
Volume of Diluent Dioxane	:	350 ml.	:	330 ml.
Added Inert Atmosphere, lbs. per sq. in., cold	::	500 lbs. of N_2	:	500 lbs. of N_2
Reaction Time	:	8 hours	:	8 hours
Reaction Temperature	:	275°	:	185-205°

TABLE XIV

SYNTHESIS OF 2-METHYLPIPERAZINE

Yield Data

	1. Copper-Chromium Oxide Experiment	2. Raney Nickel Experiment
Amount of Reactant Used, grams :	59 :	550
" " " " , moles :	0.50 :	4.65
Recovered Starting Material, grams :	--- :	144
moles :	--- :	1.22
Yield of 2-Methylpiperazine, grams :	25 :	243
moles :	0.25 :	2.43
Percentage Yield :	50% :	52.2%
Percentage Yield based on Unrecovered Starting Material:	50% :	70.7%

TABLE XV

DERIVATIVES OF 2-METHYLPIPERAZINE

Derivative	Melting Point	Reference
Picrate	dec. 272-73°	(132)
Chloroaurate	m. p. 220° (dec.) darkens 225°; dec. 235°	(80) (145)
Chloroplatinate	blackens 270°	(146)
Dihydrochloride	m. p. 248-249°	(132)
Dibenzoyl deriv.	m. p. 150°	(145)
Di-p-Toluenesulfonyl deriv.	m. p. 174°	(80)
Dinitroso deriv.	m. p. 71°	(132)
Diphenylurea	m. p. 212°	(2)
Diphenylthiourea	m. p. 189.0-189.2° (corr.)	(p. 78)

3. Synthesis of 2-Phenylpiperazine

The hitherto unknown 2-phenylpiperazine was prepared from N-(β-hydroxy-β-phenylethyl) ethane diamine by the ring-closure reaction which has been described and which was applied to the synthesis of piperazine and 2-methylpiperazine. The preparation of the starting material has been described (p. 64).

166 grams (0.92 mole) of N-(β-hydroxy-β-phenylethyl) ethane diamine dissolved in 300 ml. of dioxane was shaken with 50 grams of Raney nickel catalyst in the autoclave for three and one-half hours, at a temperature of 220°. After filtration from the catalyst the reaction mixture was fractionally distilled, first at atmospheric pressure to remove dioxane, then at reduced pressure. 52 Grams of crude 2-phenylpiperazine, b. p. 124-146°/15 mm., was collected, a yield of 35%. The yellow oil, $n_D^{30} = 1.5750$, solidified in the ice-box to a solid which was mushy at room temperature.

The experiment was repeated with 68 grams (0.38 mole) of amino-alcohol in 300 ml. of dioxane, using 10 grams of Raney nickel. The reaction was carried out at 220° for four hours. The 22 grams of crude product, b. p. 136-152°/10 mm., was a yield of 36%.

68 grams of the combined yields was purified by redistillation, yielding 40 grams of b. p. 138-145°/15 mm., the main portion of which distilled at 138°/15 mm. Recrystallization from hexane yielded 20 grams of yellowish-white solid, m. p. 65-78°. After two more recrystallizations from hexane, the melting point was 87.5-87.8° (corr.).

The dihydrochloride was prepared from a small portion of the amine; it was crystallized by adding alcohol to the aqueous solution, and it was recrystallized from aqueous alcohol. M. p., ca. 228° (dec.).

Analysis of dihydrochloride (by gravimetric precipitation of AgCl, after drying the dihydrochloride in vacuum over phosphorus pentoxide for one hour):

	Found	Calculated
Chlorine:	29.87%	30.16%

1,4-Diacetyl-2-phenylpiperazine.--2 Grams of 2-phenylpiperazine dissolved in 12 ml. of dioxane was warmed with 2 ml. of acetic anhydride for several minutes. The cooled mixture was poured into 50 ml. of ice-water mixture. The white crystalline solid which separated was recrystallized from 50% alcohol, then recrystallized twice from hexane, m. p. 70.1-71.6° (corr.).

1,4-dinitroso-2-phenylpiperazine.--1 Gram of 2-phenylpiperazine dissolved in 50 ml. of dil. hydrochloric acid was cooled to 0-10° and treated with 2 grams of sodium nitrite. A gummy material separated out, which formed a flaky precipitate after standing awhile. The solution was neutralized with potassium hydroxide and was made faintly acid with hydrochloric acid. The voluminous white precipitate which formed was filtered, air-dried, and extracted with hot hexane after adding some solid sodium bicarbonate to neutralize any hydrogen chloride present as nitrosamine hydrochloride. The crystals which separated from the hexane on cooling were purified by precipitation from methanol solution by addition of water, yielding a product of m. p. 69.6-70.2°. After another purification by precipitation from methanol, the melting point of the pearly white leaflets was 68.9-70.2° (corr.).

Picrate of 2-phenylpiperazine.--1 gram of 2-phenylpiperazine dissolved in 95% alcohol was added to 25 ml. of a saturated solution of picric acid in alcohol. The precipitate was filtered, washed on the filter, and boiled with 200 ml. of aqueous alcohol. The mixture was filtered hot. The picrate which crystallized from the filtrate on cooling was filtered, washed on the filter with alcohol, and air-dried. The melting point was ca. 272° (dec.) (corr.).

Summary of Properties of 2-Phenylpiperazine.

Physical State: white crystalline solid with a slight amine odor.

Empirical Formula: $C_{10}H_{14}N_2$

Structural Formula:

Molecular Weight:	162.23
Melting Point:	87.8-87.2° (corr.)
Boiling Point:	156°/10 mm. (corr.)

Summary of Derivatives of 2-Phenylpiperazine.

Dihydrochloride:	m. p. ca. 335° (dec.)
Diacetyl deriv.	m. p. 70.1-71.2° (corr.)
Dinitroso deriv.:	m. p. 68.9-70.2° (corr.)
Picrate:	m. p. ca. 272° (dec.) (corr.)

4. Summary

Two substituted piperazines have been prepared by the ring-closure reaction described in part A, indicating the generality of the reaction. 2-Phenylpiperazine was synthesized and characterized. 2-Methylpiperazine was prepared; and the process under discussion is compared with the methods which have been used previously for the synthesis of 2-methylpiperazine. A survey is given of the reactions which have been utilized for synthesizing carbon-substituted piperazines.

III. MOLAR REFRACTION DATA

The molecular refraction is an additive and constitutive property of matter which is of particular value in the study of the structures of organic compounds. The measurements can be made quickly and easily. The molecular refraction is independent of temperature; and the measurements may be made at room temperature.

Molecular refractions are given here (Table XVI) for the liquid amino-alcohols which were described in the preceding pages. The experimental values compare well with the calculated values, the maximum variation being 3.5 parts in 1000. These constitute additional evidence of the structures of these amino-alcohols, some of which have not been described previously in the literature.

The theoretical values listed in Table XVI were calculated from the refraction equivalents for atoms which were reported by Auwers and Eisenlohr (8). These values, given in Table XVII as listed by Gilman (60), are for refractive measurements made with the D line of sodium.

The experimental values were obtained by use of the equation of Lorentz (88) and Lorenz (89),

$$R = \frac{n^2-1}{n^2+2} \cdot \frac{M}{d}$$

in which n, M, and d are the refractive index, molecular weight, and density, respectively, of the compound which the molecular refraction R. The refractive index measurements were made with a Spencer Abbe Refractometer, using daylight or electric illumination. The values given, the corrected scale readings, represent values for the D line of sodium.

TABLE XVI

MOLECULAR REFRACTIONS

Compound	Empirical Formula	Molecular Weight M	t	d_4^t	n_D^t	R Exp.	R Calc.	Deviation, parts per 1000
N-(β Hydroxyethyl) Ethane Diamine	$C_4H_{12}N_2O$	104.15	25°	1.0264	1.4861	28.12	28.22	-3.5
N-(β Hydroxypropyl) Ethane Diamine	$C_5H_{14}N_2O$	118.18	25°	0.9667	1.4738	33.78	33.84	-1.6
			28.8°	0.9610	1.4728	33.79		-1.5
N-(β Hydroxy-β-Methyl) Ethane Diamine	$C_6H_{16}N_2O$	132.21	25°	0.9556	1.4672	36.40	36.45	-1.3
1-(β Hydroxyethyl)-Piperazine	$C_6H_{14}N_2O$	130.18	20°	1.0636	1.5060	36.63	36.77	-3.8
			25°	1.0641	1.5055	36.65		-3.5
1-(β Hydroxypropyl)-Piperazine	$C_7H_{16}N_2O$	144.21	20°	1.0108	1.4921	41.42	41.39	+1.0

TABLE XVII

ATOMIC REFRACTION EQUIVALENTS

Group	Value (D line of Na)
C	2.418
H	1.100
O (hydroxyl)	1.525
N (pri.-amine)	2.322
N (sec.-amine)	2.499
N (tert.-amine)	2.480

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VI. BIOGRAPHICAL ITEMS

Leland J. Kitchen was born February 19, 1917 at Sentinel Butte, North Dakota. He attended elementary school at Bismarck, North Dakota and received part of his high school education in that city. He was graduated from the Fort Myers, Florida High School in 1933. He has attended the University of Florida since 1933, where he received the degree of Bachelor of Science with High Honors in 1939.

Mr. Kitchen has been Student Assistant and Graduate Assistant in Chemistry for the past six years. He is a member of the American Chemical Society and is member of Phi Eta Sigma, Phi Kappa Phi and Phi Beta Kappa Honor Societies.

VII. COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date Feb 5, 1943

T. M. Simpson
Dean

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